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Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.

(54) Title: GENES OF THE 1-DESOXY-D-XYLULOSE BIOSYNTHETIC PATHWAY

(54) Bezeichnung: GENE DES 1-DESOXY-D-XYLULOSE-BIOSYNTHESEWEGS

(57) Abstract

The invention relates to the 1-desoxy- D-xylulose- 5-phosphate reductoisomerase gene, the 1-desoxy- D-xylulose- 5-phosphate-synthase gene and the gcpE gene of the 1-desoxy- D-xylulose biosynthetic pathway and to their use for transforming vectors, host organisms and plants and for determining substances that inhibit this biosynthetic pathway.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft das 1-Desoxy- D-xylulose- 5-phosphatreduktoisomerase -Gen, das 1-Desoxy- D-xylulose-5-phosphat- Synthase- Gen und das gcpE-Gen des 1-Desoxy- D-xylulose- Biosynthesewegs und ihre Verwendung zur Transformation von Vektoren, Wirtsorganismen und Pflanzen und zur Bestimmung von Stoffen, die diesen Biosyntheseweg inhibieren.

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Gene des 1-Desoxy-D-xylulose-Biosynthesewegs

Die vorliegende Erfindung betrifft DNA-Sequenzen, die bei Integration in das Genom von Viren, Eukaryonten und Prokaryonten die Isoprenoid-Biosynthese verändern sowie gentechnologische Verfahren zur Herstellung dieser transgenen Viren, Eukaryonten und Prokaryonten. Außerdem betrifft sie Verfahren zur Identifiziereung von Stoffen mit herbizider, antimikrobieller, antiparasitärer, antiviraler, fungizider, bakterizider Wirkung bei Pflanzen und antimikrobieller, antiparasitärer, antimykotischer, antibakterieller und antiviraler Wirkung bei Mensch und Tier.

Der Biosyntheseweg zur Bildung von Isoprenoiden über den klassischen Acetat/ Mevalonat-Weg und einen alternativen, Mevalonat-unabhängigen Biosyntheseweg, den Desoxy-D-xylulose-Phosphat-Weg, ist bereits bekannt (Rohmer, M., Knani, M., Simonin, P., Sutter, B., and Sahm, H. (1993): Biochem. J. 295: 517-524).

Es ist aber nicht bekannt, wie und über welche Wege in Viren, Eukaryonten und Prokaryonten eine Änderung der Isoprenoidkonzentration über den Desoxy-D-xylulose-Phoshat-Weg erreicht werden kann. In Fig. 1 ist dieser Biosyntheseweg dargestellt.

Es werden daher DNA-Sequenzen zur Verfügung gestellt, die für die 1-Desoxy-D-xylulose-5-phosphat-Synthase (DOXP-Synthase), : 1-Desoxy-D-xylulose-5-phosphatreduktoisomerase(DOXP-Reduktoisomerase) oder das gcpE-Protein kodieren. Alle drei Gene und Enzyme sind an der Isoprenoid-Biosynthese beteiligt.

Das gcpE-Protein hat eine Kinasefunktion und katalysiert die Phosphorylierung eines Zuckers oder eines Phosphorzuckers oder einer Vorstufe der Isoprenoidbiosynthese, insbesondere die Phosphorylierung von 2-C-Methyl-D-erythritol, 2-C-Methyl-D-erythritol-phosphat, insbesondere 2-C-Methyl-D-erythritol-4-phosphat, 2-C-Methyl-D-erythrose, 2-C-Methyl-D-erythrose-

phosphat, insbesondere 2-C-Methyl-D-erythrose-4-phosphat. In der Vorstufe der Isoprenoidsynthese katalysiert das gcpE-Protein insbesondere die Phosphorylierung der folgenden Substanzen:
$CH_2(OH)-C(CH_3)=C(OH)-CH_2-O-PO(OH)_2$, $CH_2(OH)-C(CH_3)=C(OH)-CH_2-OH$,
$CH_2(OH)-CH(CH_3)-CO-CH_2-O-PO(OH)_2$, $CH_2(OH)-CH(CH_3)-CO-CH_2-OH$
$CH_2=C(CH_3)-CO-CH_2-O-PO(OH)_2$, $CH_2=C(CH_3)-CO-CH_2-OH$,
$CH_2=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$, $CH_2=C(CH_3)-CH(OH)-CH_2-OH$,
$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-O-PO(OH)_2$, $CH_2(OH)-C(=CH_2)-C(OH)-CH_2-OH$
$CHO-CH(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$, $CHO-CH(CH_3)-CH(OH)-CH_2-OH$,
$CH_2(OH)-C(OH)(CH_3)-CH=CH-O-PO(OH)_2$, $CH_2(OH)-C(OH)(CH_3)-CH=CH-OH$
$CH(OH)=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$, $CH(OH)=C(CH_3)-CH(OH)-CH_2-OH$,
$(CH_3)_2HC-CO-CH_2-O-PO(OH)_2$, $(CH_3)_2HC-CO-CH_2-O-H$,
$(CH_3)_2HC-CH(OH)-CH_2-O-PO(OH)_2$, $(CH_3)_2HC-CH(OH)-CH_2-O-H$.

Die DOXP-Synthase katalysiert die Kondensation von Pyruvat und Glyceraldehyd-3-phosphat zu 1-Deoxy-D-xylulose-5-phosphat und die DOXP-Reduktoisomerase katalysiert die Umwandlung von 1-Deoxy-D-xylulose-5-phosphat zu 2-C-Methyl-D-erythritol-4-phosphat. (siehe Fig. 1).

Die Erfindung betrifft die folgenden DNA-Sequenzen:
DNA-Sequenzen, die für ein Polypeptid mit der in SEQ ID NO:2 dargestellten Aminosäuresequenz codieren oder für ein Analoges oder Derivat des Polypeptids gemäß SEQ ID NO:2, worin eine oder mehrere Aminosäuren deletiert, hinzugefügt oder durch andere Aminosäuren substituiert worden sind,

DNA-Sequenzen, die für ein Polypeptid mit der in SEQ ID NO:4 dargestellten Aminosäuresequenz codieren oder für ein Analoges oder Derivat des Polypeptids gemäß SEQ ID NO:4, worin eine oder mehrere Aminosäuren deletiert, hinzugefügt oder durch andere Aminosäuren substituiert worden sind,

sowie DNA-Sequenzen, die für ein Polypeptid mit der in SEQ ID NO: 6 dargestellten Aminosäuresequenz codieren oder für ein Analoges oder Derivat des Polypeptids gemäß SEQ ID NO: 6, worin eine oder mehrere Aminosäuren deletiert, hinzugefügt oder durch andere Aminosäuren substituiert worden sind.

Die Gene und ihre Genprodukte (Polypeptide) sind im Sequ nzprotokoll mit ihrer Primärstruktur aufgeführt und haben folgende Zuordnung:
SEQ ID NO:1: 1-Desoxy-D-xylulose-5-phosphatreduktoisomerase-Gen
SEQ ID NO:2: 1-Desoxy-D-xylulose-5-phosphatreduktoisomerase
SEQ ID NO:3: 1-Desoxy-D-xylulose-5-phosphat-Synthase-Gen
SEQ ID NO:4: 1-Desoxy-D-xylulose-5-phosphat-Synthase
SEQ ID NO:5: gcpE-Gen
SEQ ID NO:6 : gcpE-Proteine.

Die DNA-Sequenzen stammen alle aus Plasmodium falciparum.

Außer den im Sequenzprotokoll genannten DNA-Sequenzen sind auch solche geeignet, die infolge der Degeneration des genetischen Codes eine andere DNA-Sequenz besitzen, jedoch für das gleiche Polypeptid oder für ein Analoges oder Derivat des Polypeptids kodieren, worin eine oder mehrere Aminosäuren deletiert, hinzugefügt oder durch andere Aminosäuren substituiert worden sind.

Die erfindungsgemäßen Sequenzen eignen sich für die Expression von Genen in Viren, Eukaryonten und Prokaryonten, die für die Isoprenoid-Biosynthese des 1-Desoxy-D-xylulose-Wegs verantwortlich sind.

Erfindungsgemäß gehören zu den Eukaryonten oder eukaryontischen Zellen tierischen Zellen, Pflanzenzellen, Algen, Hefen, Pilze und zu den Prokaryonten oder prokaryontischen Bakterien Archaebakterien und Eubakterien.

Bei Integration einer DNA-Sequenz in ein Genom, auf der eine der oben angegebenen DNA-Sequenzen lokalisiert ist, wird die Expression der oben beschriebenen Gene in Viren, Eukaryonten und Prokaryonten ermöglicht. Die erfindungsgemäß transformierten Viren, Eukaryonten und Prokaryonten werden in an sich bekannter Weise gezüchtet und das währenddessen gebildete Isoprenoid isoliert und gegebenenfalls gereinigt. Nicht alle Isoprenoide müssen isoliert werden, da die Isoprenoide in einigen Fällen direkt in die Raumluft abgegeben werden.

Die Erfindung betrifft ferner ein Verfahren zur Herstellung von transgenen Viren, Eukaryonten und Prokaryonten zur Veränderung des Isoprenoid-Gehaltes, das die folgenden Schritte enthält.

a) Herstellung einer DNA-Sequenz mit folgenden Teilsequenzen
   i) Promotor, der in Viren, Eukaryonten und Prokaryonten aktiv ist und die Bildung einer RNA im vorgesehenen Zielgewebe oder den Zielzellen sicherstellt,
   ii) DNA-Sequenz, die für ein Polypeptid mit der in SEQ ID NO:2,4 oder 6 dargestellten Aminosäuresequenz codieren oder für ein Analoges oder Derivat des Polypeptids gemäß SEQ ID NO:2,4 oder 6,
   iii) 5`- und 3`-nichttranslatierte Sequenz, die in Viren, Eukaryonten und Prokaryonten die Expression der bezeichneten Gene ermöglichen oder verbessern,
b) Transfer und Einbau der DNA-Sequenz in das Genom von Viren, prokaryontischen oder eukaryontischen Zellen mit oder ohne Verwendung eines Vektors (z.B. Plasmid, virale DNA).

Aus derart transformierten Pflanzenzellen können die intakten ganzen Pflanzen regeneriert werden.

Die für die Proteine kodierenden Sequenzen mit den Nukleotidabfolgen Seq ID NO:1, Seq ID NO:3 und Seq ID NO: 5 können mit einem die Transkription in bestimmten Organen oder Zellen sicherstellenden Promotor versehen werden, der in sense-Orientierung (3`-Ende des Promotors zum 5`-Ende der kodierenden Sequenz) an die Sequenz, die das zu bildende Protein kodiert, gekoppelt ist. An das 3`-Ende der kodierenden Seqeunz wird ein die Termination der mRNA-Synthese bestimmendes Terminationssignal angehängt. Um das zu exprimierende Protein in bestimmte subzelluläre Kompartimente, wie Chloroplasten, Amyloplasten, Mitochondrien, Vakuole, Cytosol oder Interzellularräume zu dirigieren, kann zwischen den Promotor und die kodierende Sequenz noch eine für eine sogenannte Signalsequenz oder ein Transitpeptid kodierende Sequenz gesetzt werden. In einigen Fällen ist es erforderlich, Sequenzen einzufügen, die für eine Signalsequenz am COOH-Terminus des Proteins kodieren. Die Sequenz muß im glei-

chen Leserahmen wie die kodierende Sequenz des Proteins sein. Zur Vorbereitung der Einführung der erfindungsgemäßen DNA-Sequenzen in höhere Pflanzen sind eine große Anzahl von Klonierungsvektoren verfügbar, die ein Replikationssignal für E.coli und einen Marker beinhalten, der eine Selektion der transformierten Zellen erlaubt. Je nach Einführungsmethode gewünschter Gene in die Pflanze können weitere DNA-Sequenzen erforderlich sein. Werden zum Beispiel für die Transformation der Pflanzenzelle das Ti- oder Ri-Plasmid verwendet, so muß mindestens eine rechte Begrenzung, häufig jedoch die rechte und die linke Begrenzung der Ti- und Ri-Plasmid T-DNA als Flankenbereich den einzuführenden Genen eingefügt werden. Die Verwendung von T-DNA für die Transformation von Pflanzenzellen ist intensiv untersucht und ausreichend in EP 120516; Hoekama, in: The Binary Plant Vector System, Offset-drukkerij Kanters B.V. Alblasserdam (1985), Chapter V; Fraley et al., Crit.Rev.Plant Sci. 4,1-46 und An et al. (1985) EMBO J. 4, 277-287 beschrieben worden. Ist die eingeführte DNA einmal im Genom integriert, so ist sie in der Regel stabil und bleibt auch in den Nachkommen der ursprünglich transformierten Zellen erhalten. Sie erhält normalerweise einen Selektionsmarker, der den transformierten Pflanzenzellen Resistenz gegenüber einem Biozid oder einem Antibiotikum, wie Kanamycin, G 418, Bleomycin, Hygromycin oder Phosphinotricin u.a. vermittelt. Der individuell verwendete Marker sollte daher die Selektion transformierter Zellen gegenüber Zellen, denen die eingefügte DNA fehlt, gestatten.

Für die Einführung von DNA in eine Pflanze stehen viele Techniken zur Verfügung. Diese Techniken umfassen die Transformation mit Hilfe von Agrobakterien, z.B. Agrobacterium tumefaciens , die Fusion von Protoplasten, die Mikroinjektion von DNA, die Elekroporation, sowie ballistische Methoden und die Virusinfektion. Aus dem transformierten Pflanzenmaterial können dann im geeigneten Medium, welches Antibiotika oder Biozide zur Selektion enthalten kann, wieder ganze Pflanzen regeneriert werden. Bei der Injektion und Elektroporation sind an sich keine speziellen Anforderungen an die Plasmide gestellt. Sollen aber aus derartig transformierten Zellen ganze Pflanzen regeneriert werden, ist die Anwesenheit eines selektierbaren Markergens not-

wendig. Die transformierten Zellen wachsen innerhalb der Pflanzen in der üblichen Weise (McCormick et al. (1986), Plant Cell Reports 5, 81-84). Die Pflanzen können normal angezogen werden und mit Pflanzen, die die gleiche transformierte Erbanlage oder andere Erbanlagen haben, gekreuzt werden. Die daraus entstehenden Individuen haben die entsprechenden phänotypischen Eigenschaften.

Weiterhin sind Gegenstand der Erfindung Expressionsvektoren, die eine oder mehrere der erfindungsgemäßen DNA-Sequenzen enthalten. Solche Expressionsvektoren erhält man, indem man die erfindungsgemäßen DNA-Sequenzen mit geeigneten funktionellen Regulationssignalen versieht. Solche Regulationssignale sind DNA-Sequenzen, die für die Expression verantwortlich sind, beispielsweise Promotoren, Operatoren, Enhancer, ribosomale Bindungsstellen, und die vom Wirtsorganismus erkannt werden.

Gegebenenfalls können noch weitere Regulationssignale, die beispielsweise Replikation oder Rekombination der rekombinanten DNA im Wirtsorganismus steuern, Bestandteil des Expressionsvektors sein.

Ebenso gehören die mit den erfindungsgemäßen DNA-Sequenzen oder Expressionsvektoren transformierten Wirtsorganismen zum Gegenstand der Erfindung.

Für die Expression der erfindungsgemäßen Enzyme eignen sich besonders solche Wirtszellen und Organismen, die keine intrinsischen Enzyme mit der Funktion der DOXP-Synthase, der DOXP-Reduktoisomerase oder des gcpE-Proteins aufweisen. Dies trifft für Archaebacterien, Tiere, Pilze, Schleimpilze und einige Eubakterien zu. Durch das Fehlen dieser intrinsischen Enzymaktivitäten wird die Detektion und Aufreinigung der rekombinanten Enzyme wesentlich erleichtert. Auch wird es erst dadurch möglich, mit geringem Aufwand die Aktivität und insbesondere die Hemmung der Aktivität der erfindungsgemäßen rekombinanten Enzyme durch verschiedenen Chemikalien und Pharmaka in Rohextrakten aus den Wirtszellen zu messen.

Die Expression der erfindungsgemäßen Enzyme erfolgt vorteilhafterweise dann in eukaryontischen Zellen, wenn posttranslatorische Modifikationen und eine native Faltung der Polypeptidkette erreicht werden soll. Außerdem wird in Abhängigkeit vom Expressionssystem bei der Expression genomischer DNA-Sequenzen erreicht, daß Introns durch Spleißen der DNA beseitigt und die Enzyme in der für die Parasiten charakteristischen Polypeptidsequenz produziert werden. Für Introns codierende Sequenzen können auch durch rekombinante DNA-Technologie aus den zu exprimierenden DNA-Sequenzen beseitigt oder experimentell eingefügt werden.

Die Isolierung des Proteins kann aus der Wirtszelle oder dem Kulturüberstand der Wirtszelle nach dem Fachmann bekannten Verfahren erfolgen. Es kann auch eine in vitro Reaktivierung der Enzyme erforderlich sein.

Zur Erleichterung der Aufreinigung können die erfindungsgemäßen Enzyme oder Teilsequenzen der Enzyme als Fusionsprotein mit verschiedenen Peptidketten exprimiert werden. Dazu eigenen sich besonders Oligo-Histidin-Sequenzen und Sequenzen, die von der Glutathion-S-Transferase, Thioredoxin oder Calmodulin-bindenden Peptiden abgeleitet sind.

Weiterhin können die erfindungsgemäßen Enzyme oder Teilsequenzen der Enzyme als Fusionsprotein mit solchen, dem Fachmann bekannten, Peptidketten exprimiert werden, daß die rekombinanten Enzyme in das extrazelluläre Millieu oder in bestimmte Kompartimente der Wirtszellen transportiert werden. Dadurch kann sowohl die Aufreinigung, als auch die Untersuchung der biologischen Aktivität der Enzyme erleichtert werden.

Bei der Expression der erfindungsgemäßen Enzyme kann es sich als zweckmäßig erweisen, einzelne Codone zu verändern. Dabei

ist der gezielte Austausch von Basen in der kodierenden Region auch sinnvoll, wenn die genutzten Codone in den Parasiten abweichend sind von der Codonnutzung im heterologen Expressionssystem, um eine optimale Synthese des Proteins zu gewährleisten.

Weiterhin können die erfindungsgemäßen Enzyme unter standardisierten Bedingungen durch dem Fachmann bekannte Techniken durch in vitro-Translation gewonnen werden. Dafür geeignete Systeme sind Kaninchen-Reticulozyten- und Weizenkeimextrakte und Bakterienlysate. Auch kann in vitro transskribierte mRNA in Xenopus-Oocyten translatiert werden.

Durch chemische Synthese können Oligo- und Polypeptide hergestellt werden, deren Sequenzen aus der Peptidsequenz der erfindungsgemäßen Enzyme abgeleitet sind. Bei geeigneter Wahl der Sequenzen besitzen derartige Peptide Eigenschaften, die für die erfindungsgemäßen Enzyme charakteristisch sind. Derartige Peptide können in großen Mengen hergestellt werden und eignen sich besonders für Studien über die Kinetik der Enzymaktivität, die Regulation der Enzymaktivität, die dreidimensionale Struktur der Enzyme, die Hemmung der Enzymaktivität durch verschiedenen Chemikalien und Pharmaka und die Bindungsgeometrie und Bindugnsaffinität verschiedener Liganden.

Vorzugsweise wird zur rekombinanten Herstellung der erfindungsgemäßen Enzyme eine DNA mit den Nukleotiden aus den Sequenzen SEQ ID NO: 1, 3 und 5 verwendet.

Die Erfindung umfaßt daher außerdem ein Verfahren zum Screening nach Verbindungen, die desDesoxy-D-xylulose-Phosphat-Stoffwechselweg inhibieren. Gemäß diesem Verfahren wird ein Wirtsorganismus, der einen rekombinanten Expressionsvektor enthält, wobei der Vektor zumindest einen Teil der Oligonukleotidsequenz gemäß SEQ ID NO:1, SEQ ID NO: 3 oder SEQ ID NO: 5 oder Varianten oder Homologe dieser aufweist, und außerdem eine

Verbindung, von der vermutet wird, daß sie eine antimikrobielle, antiparasitäre, antibakterielle, antivirale und antimykotische Wirkung bei Mensch und Tier oder eine antimikrobielle, antivirale, bakterizide, herbizide oder fungizide Wirkung bei Pflanzen hat, bereitgestellt. Anschließend wird der Wirtsorganismus mit der Verbindung in Kontakt gebracht und die Wirksamkeit der Verbindung bestimmt.

Ein weiterer Gegenstand dieser Erfindung sind Methoden zur Bestimmung der enzymatische Aktivität des gcpE-Proteins. Diese kann nach bekannten Verfahren bestimmt werden. Hierbei wird die Phosphorylierung eines Zuckers oder eines Phosphorzuckers oder einer Vorstufe der Isoprenoidbiosynthese, insbesondere die Phosphorylierung von 2-C-Methyl-D-erythritol, 2-C-Methyl-D-erythritol-phosphat, insbesondere 2-C-Methyl-D-erythritol-4-phosphat, 2-C-Methyl-D-erythrose, 2-C-Methyl-D-erythrose-phosphat, insbesondere 2-C-Methyl-D-erythrose-4-phosphat, detektiert. Ein weiterer Gegenstand dieser Erfindung ist die Verwendung dieser Meßverfahren zur Ermittlung von Stoffen, die die Aktivität der jeweiligen Enzyme inhibieren.

Die enzymatische Aktivität von DOXP-Synthase und DOXP-Reduktisomerase kann in einem einzigen Schitt detektiert werden, indem die Umwandlung von Glycerinaldehyd-3-phosphat zu 2-C-Methylerythritol-4-phosphat bestimmt wird.

Analog erfolgt die Bestimmung der Aktivitäten von DOXP-Synthase und DOXP-Reduktoisomerase. Für die Bestimmung der DOXP-Synthase-Aktivität eignen sich auch fluorimetrische Verfahren, wie von Querol et al. beschrieben (Querol et al. Abstracts 4th european symposium on plant isoprenoids, Barcelona 21-23 April 1999).

Patentansprüche

1. DNA-Sequenzen, die für ein Polypeptid mit der in SEQ ID NO: 2 dargestellten Aminosäuresequenz codieren oder für ein Analoges oder Derivat des Polypeptids gemäß SEQ ID NO:2, worin eine oder mehrere Aminosäuren deletiert, hinzugefügt oder durch andere Aminosäuren substituiert worden sind.

2. DNA-Sequenzen, die für ein Polypeptid mit der in SEQ ID NO: 4 dargestellten Aminosäuresequenz codieren oder für ein Analoges oder Derivat des Polypeptids gemäß SEQ ID NO:4, worin eine oder mehrere Aminosäuren deletiert, hinzugefügt oder durch andere Aminosäuren substituiert worden sind.

3. DNA-Sequenzen, die für ein Polypeptid mit der in SEQ ID NO: 6 dargestellten Aminosäuresequenz codieren oder für ein Analoges oder Derivat des Polypeptids gemäß SEQ ID NO: 6, worin eine oder mehrere Aminosäuren deletiert, hinzugefügt oder durch andere Aminosäuren substituiert worden sind.

4. DNA-Sequenz gemäß einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß sie außerdem funktionelle Regulationssignale, insbesondere Promotoren, Operatoren, Enhancer, ribosomale Bindungsstellen, aufweist.

5. DNA-Sequenz mit folgenden Teilsequenzen
   i) Promotor, der in Viren, Eukaryonten und Prokaryonten aktiv ist und die Bildung einer RNA im vorgesehenen Zielgewebe oder den Zielzellen sicherstellt,
   ii) DNA-Sequenzen gemäß einem der Ansprüche 1 bis 3,
   iii) 3`-nichttranslatierte Sequenz, die in Viren, Eukaryonten und Prokaryonten zur Addition von Poly-A Resten an das 3`-Ende der RNA führt.

6. Verfahren zur Herstellung von transgenen Viren, Eukaryonten und Prokaryonten zur Veränderung des Isoprenoid-Gehaltes, dadurch gekennzeichnet, daß eine DNA-Sequenz gemäß Anspruch 4 oder 5 in das Genom von Viren, eukaryontischen und proka-

ryontischen Zellen mit oder ohne Verwendung eines Vektors transferiert und eingebaut wird.

7. Transgene Systeme, insbesondere Pflanzen und Pflanzenzellen, welche ein oder mehrere DNA-Sequenzen gemäß der Ansprüche 1 bis 5 als „fremde" oder „zusätzliche" DNA enthalten, die exprimiert werden.

8. Expressionsvektor, enthaltend eine oder mehrere DNA-Sequenzen gemäß Anspruch 1 bis 5.

9. Protein, welches am 1-Deoxy-D-Xylulose-5-Phosphat-Stoffwechselweges beteiligt ist und a) codiert wird von den DNA-Sequenzen SEQ ID NO: 1,3 oder 5 oder b) codiert wird von DNA-Sequenzen, die mit den DNA-Sequenzen SEQ ID NO: 1,3,5 oder Fragmenten dieser DNA-Sequenzen im DNA-Bereich, der für das reife Protein codiert, hybridisieren.

10. Protein nach den Anspruch 9, erhältlich aus den Kulturüberständen von Parasiten oder aus den aufgeschlossenen Parasiten und Aufreinigung über chromatographische und elektrophoretische Techniken.

11. Protein nach einem der Ansprüche 9 und 10, dadurch gekennzeichnet, daß es a) das Produkt einer viralen, prokaryontischen oder eukaryontischen Expression einer exogenen DNA ist, b) codiert wird von den Sequenzen SEQ ID NO: 1, 3 oder 5 oder codiert wird von DNA-Sequenzen, die mit den in den DNA-Sequenzen SEQ ID NO: 1, 3 oder 5 oder Fragmenten dieser DNA-Sequenzen im DNA-Bereich, der für das reife Protein kodiert, hybridisieren, oder c) codiert wird von DNA-Sequenzen, die ohne Degeneration des genetischen Codes mit den in b) definierten Sequenzen hybridisieren würden und für ein Polypeptid mit entsprechender Aminosäure-Sequenz kodieren.

12. Protein gemäß einem der vorangehenden Ansprüchen, dadurch gekennzeichnet, daß es die Aminosäuresequenzen SEQ ID NO: 2, 4 oder 6 aufweist.

13. Verfahren zur Bestimmung der enzymatischen Aktivität des gcpE-Proteins, dadurch gekennzeichnet, daß Phosphorylierung eines Zuckers oder eines Phosphorzuckers oder einer Vorstufe der Isoprenoidbiosynthese, insbesondere die Phosphorylierung von 2-C-Methyl-D-erythritol, 2-C-Methyl-D-erythritol-phosphat, insbesondere 2-C-Methyl-D-erythritol-4-phosphat, 2-C-Methyl-D-erythrose, 2-C-Methyl-D-erythrose-phosphat, insbesondere 2-C-Methyl-D-erythrose-4-phosphat, und der Phosphat- und Alkoholvorstufen, detektiert wird.

14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß die Phosphorylierung der folgenden Phosphate oder Alkohole detektiert wird:
$CH_2(OH)-C(CH_3)=C(OH)-CH_2-O-PO(OH)_2$,
$CH_2(OH)-C(CH_3)=C(OH)-CH_2-OH$,
$CH_2(OH)-CH(CH_3)-CO-CH_2-O-PO(OH)_2$, $CH_2(OH)-CH(CH_3)-CO-CH_2-OH$
$CH_2=C(CH_3)-CO-CH_2-O-PO(OH)_2$, $CH_2=C(CH_3)-CO-CH_2-OH$,
$CH_2=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$, $CH_2=C(CH_3)-CH(OH)-CH_2-OH$,
$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-O-PO(OH)_2$,
$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-OH$
$CHO-CH(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$, $CHO-CH(CH_3)-CH(OH)-CH_2-OH$,
$CH_2(OH)-C(OH)(CH_3)-CH=CH-O-PO(OH)_2$,
$CH_2(OH)-C(OH)(CH_3)-CH=CH-OH$
$CH(OH)=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$,
$CH(OH)=C(CH_3)-CH(OH)-CH_2-OH$,
$(CH_3)_2HC-CO-CH_2-O-PO(OH)_2$,
$(CH_3)_2HC-CO-CH_2-O-H$,
$(CH_3)_2HC-CH(OH)-CH_2-O-PO(OH)_2$,
$(CH_3)_2HC-CH(OH)-CH_2-O-H$.

15. Verfahren zur gekoppelten Bestimmung der enzymatischen Aktivität der DOXP-Synthase und der DOXP-Reduktase, dadurch gekennzeichnet, daß die Umwandlung von Glycerinaldehyd-3-phosphat zu 2-C-Methylerythritol-4-phosphat detektiert wird.

16. Verfahren zum Screening einer Verbindung für die Therapie von infektiösen Prozessen bei Mensch und Tier, wobei das Verfahren umfaßt:
    a) Bereitstellen einer Wirtszelle, die einen rekombinanten Expressionsvektor enthält, wobei der Vektor zumindest einen Teil der Oligonukleotidsequenz gemäß SEQ ID NO:1, SEQ ID NO: 3 oder SEQ ID NO: 5 oder Varianten oder Analoga dieser aufweist, und außerdem eine Verbindung, von der vermutet wird, daß sie eine antimykotische, antibiotische, antiparasitäre oder antivirale Wirkung bei Mensch und Tier hat,
    b) In-Kontakt-Bringen der Wirtszelle mit der Verbindung und
    c) Bestimmung der antimikrobiellen, antimykotischen, antibiotischen, antiparasitären oder antiviralen Wirksamkeit der Verbindung.

17. Verfahren zum Screening nach Verbindungen zur Behandlung von Pflanzen, wobei das Verfahren umfaßt:
    a) Bereitstellen einer Wirtszelle, die einen rekombinanten Expressionsvektor enthält, wobei der Vektor zumindest einen Teil der Oligonukleotidsequenz gemäß SEQ ID NO:1, SEQ ID NO: 3 oder SEQ ID NO: 5 oder Varianten oder Analoga dieser aufweist, und außerdem eine Verbindung, von der vermutet wird, daß sie eine antimikrobielle, antivirale, antiparasitäre, bakterizide, fungizide oder herbizide Wirkung bei Pflanzen hat,
    b) In-Kontakt-Bringen der Wirtszelle mit der Verbindung und
    c) Bestimmung der antimikrobiellen, antiviralen, antiparasitären, bakteriziden, fungiziden oder herbiziden Wirksamkeit der Verbindung.

18. Verwendung von DNA nach einem der Ansprüche 1 bis 5 oder von Proteinen nach einem der Ansprüche 9 bis 12 oder von transgenen Systemen nach Anspruch 7 zur Vorbeugung oder Therapie von Erkrankungen bei Mensch und Tier.

SEQUENZPROTOKOLL

<110> Jomaa, Hassan

<120> Gene des 1-Desoxy-D-xylulose-Biosynthesewegs

<130> 15696

<140> PCT/EP99
<141> 1999-09-22

<150> DE19923567.8
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Arg Lys Asn Asn Ala Tyr Ile Asn Tyr Gly Ile Gly Tyr Asn Gly Pro
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gat aat aaa ata aca aag agt aga aga tgt aaa aga ata aag tta tgc   192
Asp Asn Lys Ile Thr Lys Ser Arg Arg Cys Lys Arg Ile Lys Leu Cys
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Lys Lys Asp Leu Ile Asp Ile Gly Ala Ile Lys Lys Pro Ile Asn Val
65                  70                  75                  80

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Ala Ile Phe Gly Ser Thr Gly Ser Ile Gly Thr Asn Ala Leu Asn Ile
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Tyr Val Asn Lys Ser Val Asn Glu Leu Tyr Glu Gln Ala Arg Glu Phe
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tta cca gaa tat ttg tgt ata cat gat aaa agt gta tat gaa gaa tta   432
Leu Pro Glu Tyr Leu Cys Ile His Asp Lys Ser Val Tyr Glu Glu Leu
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aaa gaa ctg gta aaa aat ata aaa gat tat aaa cct ata ata ttg tgt   480
Lys Glu Leu Val Lys Asn Ile Lys Asp Tyr Lys Pro Ile Ile Leu Cys
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ggt gat gaa ggg atg aaa gaa ata tgt agt agt aat agt ata gat aaa   528
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Pro Phe Gln Asn Leu Thr Met Asp Glu Leu Lys Asn Val Thr Ser Glu
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Asp Ser Ala Thr Met Met Asn Lys Gly Leu Glu Val Ile Glu Thr His
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Thr Trp Pro Asp Arg Ile Lys Thr Asn Leu Lys Pro Leu Asp Leu Ala
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Gln Val Ser Thr Leu Thr Phe His Lys Pro Ser Leu Glu His Phe Pro
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Cys Ile Lys Leu Ala Tyr Gln Ala Gly Ile Lys Gly Asn Phe Tyr Pro
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Thr Val Leu Asn Ala Ser Asn Glu Ile Ala Asn Asn Leu Phe Leu Asn
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Asn Lys Ile Lys Tyr Phe Asp Ile Ser Ser Ile Ile Ser Gln Val Leu
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gaa tct ttc aat tct caa aag gtt tcg gaa aat agt gaa gat tta atg   1392
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Gly Asp Glu Gly Met Lys Glu Ile Cys Ser Ser Asn Ser Ile Asp Lys
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Ile Val Ile Gly Ile Asp Ser Phe Gln Gly Leu Tyr Ser Thr Met Tyr
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370 375 380

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385 390 395 400

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Leu Ser Arg Lys Asn Ser Leu Cys Ser Ser Lys Asn Lys Ile Ala Cys
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80                  85                  90                  95

tat agt aat aaa ttg tac atg gat aag agg aaa aat att aat aat gta   458
Tyr Ser Asn Lys Leu Tyr Met Asp Lys Arg Lys Asn Ile Asn Asn Val
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att agt act aat aaa ata tct ggg tcc att tca aat att tgt agt aga   506
Ile Ser Thr Asn Lys Ile Ser Gly Ser Ile Ser Asn Ile Cys Ser Arg
            115                 120                 125

aat caa aaa gaa aat gaa caa aaa aga aat aaa caa aga tgt tta act   554
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        130                 135                 140

caa tgt cac act tat aat atg tca cat gaa cag gac aaa cta gct aat   602
Gln Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn
    145                 150                 155

gat aat aat agg aat aat aaa aag aat ttt aat tta tta ttt ata aat   650
Asp Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn
160                 165                 170                 175

tat ttt aat ttg aaa cga atg aaa aat tct ctt cta aat aaa gac aat   698
Tyr Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn
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aat cgt gat tca cat aaa ttg ttt tct gga gaa ttt gac gat tat aca   842
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    225                 230                 235

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Tyr Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys
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        450                 455                 460

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    465                 470                 475

tat gat aat gtt ata tat gat ata gga cat caa gca tat gta cat aag   1610
Tyr Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys
480                 485                 490                 495

ata ttg acc gga aga aaa cta tta ttt cta tca tta aga aat aaa aaa   1658
Ile Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys
                500                 505                 510

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560                 565                 570                 575

caa aaa gga ata cac aat gat aat aat att aac aat aat att aat aat   1898
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Asn Asn Tyr Ile Asn Pro Ser Asp Val Val Gly Arg Glu Asn Thr Asn
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gta cca aat gta cga aat gat aac cat aac gtg gat aaa gta cac att   1994
Val Pro Asn Val Arg Asn Asp Asn His Asn Val Asp Lys Val His Ile
        610                 615                 620

gct att ata gga gat ggt ggt tta aca ggt gga atg gca tta gaa gcg   2042
Ala Ile Ile Gly Asp Gly Gly Leu Thr Gly Gly Met Ala Leu Glu Ala
    625                 630                 635

tta aat tat att tca ttc ttg aat tct aaa att tta att att tat aat   2090
Leu Asn Tyr Ile Ser Phe Leu Asn Ser Lys Ile Leu Ile Ile Tyr Asn
640                 645                 650                 655

gat aac gga caa gtt tct tta cca aca aat gcc gta agt ata tca ggt   2138
Asp Asn Gly Gln Val Ser Leu Pro Thr Asn Ala Val Ser Ile Ser Gly
                660                 665                 670

aat aga cct ata ggt tct ata tca gat cat tta cat tat ttt gtt tct   2186
Asn Arg Pro Ile Gly Ser Ile Ser Asp His Leu His Tyr Phe Val Ser
            675                 680                 685

aat ata gaa gca aat gct ggt gat aat aaa tta tcg aaa aat gca aaa   2234
Asn Ile Glu Ala Asn Ala Gly Asp Asn Lys Leu Ser Lys Asn Ala Lys
        690                 695                 700
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gag aat aac att ttt gaa aat ttg aat tat gat tat att ggt gtt gtg   2282
Glu Asn Asn Ile Phe Glu Asn Leu Asn Tyr Asp Tyr Ile Gly Val Val
    705                 710                 715

aat ggt aat aat aca gaa gag ctc ttt aaa gta tta aat aat ata aaa   2330
Asn Gly Asn Asn Thr Glu Glu Leu Phe Lys Val Leu Asn Asn Ile Lys
720                 725                 730                 735

gaa aat aaa tta aaa aga gct act gtt ctt cat gta cgt aca aaa aaa   2378
Glu Asn Lys Leu Lys Arg Ala Thr Val Leu His Val Arg Thr Lys Lys
                740                 745                 750

tcg aat gat ttt ata aat tca aag agt cca ata agt ata ttg cac tct   2426
Ser Asn Asp Phe Ile Asn Ser Lys Ser Pro Ile Ser Ile Leu His Ser
            755                 760                 765

ata aag aaa aat gag att ttc cct ttc gat acc act ata tta aat gga   2474
Ile Lys Lys Asn Glu Ile Phe Pro Phe Asp Thr Thr Ile Leu Asn Gly
        770                 775                 780

aat att cat aag gag aac aag ata gaa gaa gag aaa aat gtg tct tca   2522
Asn Ile His Lys Glu Asn Lys Ile Glu Glu Glu Lys Asn Val Ser Ser
    785                 790                 795

tct aca aag tat gat gta aat aat aag aat aat aaa aat aat gat aat   2570
Ser Thr Lys Tyr Asp Val Asn Asn Lys Asn Asn Lys Asn Asn Asp Asn
800                 805                 810                 815

agt gaa att ata aaa tat gaa gat atg ttt tca aaa gag acg ttc aca   2618
Ser Glu Ile Ile Lys Tyr Glu Asp Met Phe Ser Lys Glu Thr Phe Thr
                820                 825                 830

gat ata tat aca aat gaa atg tta aaa tat tta aag aaa gat aga aat   2666
Asp Ile Tyr Thr Asn Glu Met Leu Lys Tyr Leu Lys Lys Asp Arg Asn
            835                 840                 845

ata ata ttc cta tct ccc gct atg tta gga gga tca gga ttg gtt aaa   2714
Ile Ile Phe Leu Ser Pro Ala Met Leu Gly Gly Ser Gly Leu Val Lys
        850                 855                 860

att agt gag cgt tat cca aat aat gta tat gat gta ggt ata gca gaa   2762
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Ile Ser Glu Arg Tyr Pro Asn Asn Val Tyr Asp Val Gly Ile Ala Glu
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caa cat tct gta act ttc gca gca gct atg gca atg aat aag aaa tta   2810
Gln His Ser Val Thr Phe Ala Ala Ala Met Ala Met Asn Lys Lys Leu
880                 885                 890                 895

aaa ata caa tta tgt ata tat tcg acc ttt tta caa aga gca tat gat   2858
Lys Ile Gln Leu Cys Ile Tyr Ser Thr Phe Leu Gln Arg Ala Tyr Asp
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caa att ata cat gat ctt aat tta caa aat ata cct tta aag gtt ata   2906
Gln Ile Ile His Asp Leu Asn Leu Gln Asn Ile Pro Leu Lys Val Ile
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att gga aga agt gga tta gta gga gag gat ggg gca aca cat caa ggt   2954
Ile Gly Arg Ser Gly Leu Val Gly Glu Asp Gly Ala Thr His Gln Gly
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ata tat gat tta tct tat ctt ggg aca ctt aac aat gca tat ata ata   3002
Ile Tyr Asp Leu Ser Tyr Leu Gly Thr Leu Asn Asn Ala Tyr Ile Ile
    945                 950                 955

tct cca agt aat caa gtt gat ttg aaa aga gct ctt agg ttt gct tat   3050
Ser Pro Ser Asn Gln Val Asp Leu Lys Arg Ala Leu Arg Phe Ala Tyr
960                 965                 970                 975

tta gat aag gac cat tct gtg tat ata cgt ata ccc aga atg aac ata   3098
Leu Asp Lys Asp His Ser Val Tyr Ile Arg Ile Pro Arg Met Asn Ile
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Glu Ser Lys Asn Ile Asp Val Asn Val Asp Ile Asn Asp Asp Val Asp
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aat gaa cat tat tca agc aga gga gat aca cag aca aaa aaa aaa aaa   3338
Asn Glu His Tyr Ser Ser Arg Gly Asp Thr Gln Thr Lys Lys Lys Lys
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gtt tgt atc ttt aac atg ggt agt atg ctt ttt aat gta att aat gct   3386
Val Cys Ile Phe Asn Met Gly Ser Met Leu Phe Asn Val Ile Asn Ala
            1075                1080                1085

ata aaa gaa att gaa aaa gaa caa tat att tca cat aat tat tct ttt   3434
Ile Lys Glu Ile Glu Lys Glu Gln Tyr Ile Ser His Asn Tyr Ser Phe
        1090                1095                1100

tca att gtt gat atg ata ttt tta aat cct tta gat aaa aat atg ata   3482
Ser Ile Val Asp Met Ile Phe Leu Asn Pro Leu Asp Lys Asn Met Ile
    1105                1110                1115

gat cat gta ata aaa caa aat aaa cat caa tat tta att act tat gaa   3530
Asp His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu
1120                1125                1130                1135

gat aat act ata ggt ggt ttt tct aca cat ttc aat aat tat tta ata   3578
Asp Asn Thr Ile Gly Gly Phe Ser Thr His Phe Asn Asn Tyr Leu Ile
                1140                1145                1150

gaa aat aat tat att aca aaa cat aac tta tat gtt cat aat att tat   3626
Glu Asn Asn Tyr Ile Thr Lys His Asn Leu Tyr Val His Asn Ile Tyr
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tta tct aat gag cca att gaa cat gca tct ttt aag gat caa caa gaa   3674
Leu Ser Asn Glu Pro Ile Glu His Ala Ser Phe Lys Asp Gln Gln Glu
        1170                1175                1180

gtc gtc aaa atg gat aaa tgt agt ctt gtc aat aga att aaa aat tat   3722
Val Val Lys Met Asp Lys Cys Ser Leu Val Asn Arg Ile Lys Asn Tyr
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Leu Lys Asn Asn Pro Thr
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Asn Gln Ile Lys Thr Glu Lys Ile Tyr Ile Lys Lys Leu Asn Arg Leu
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Ser Arg Lys Asn Ser Leu Cys Ser Ser Lys Asn Lys Ile Ala Cys Leu
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Phe Asp Ile Gly Asn Asp Asp Asn Arg Asn Thr Thr Tyr Gly Tyr Asn
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Val Asn Val Lys Asn Asp Asp Ile Asn Ser Leu Leu Lys Asn Asn Tyr
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Ser Asn Lys Leu Tyr Met Asp Lys Arg Lys Asn Ile Asn Asn Val Ile
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Ser Thr Asn Lys Ile Ser Gly Ser Ile Ser Asn Ile Cys Ser Arg Asn
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Gln Lys Glu Asn Glu Gln Lys Arg Asn Lys Gln Arg Cys Leu Thr Gln
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Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn Asp

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Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn Tyr
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Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn Phe
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Phe Tyr Cys Lys Glu Lys Lys Leu Ser Phe Leu His Lys Ala Tyr Lys
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Lys Lys Asn Cys Thr Phe Gln Asn Tyr Ser Leu Lys Arg Lys Ser Asn
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Arg Asp Ser His Lys Leu Phe Ser Gly Glu Phe Asp Asp Tyr Thr Asn
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245 250 255

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Asn Thr Phe Ile Asn Ile Asp Glu Tyr Lys Thr Ile Tyr Gly Asp Glu
325 330 335

Ile Tyr Lys Glu Ile Tyr Glu Leu Tyr Val Glu Arg Asn Ile Pro Glu
340 345 350

Tyr Tyr Glu Arg Lys Tyr Phe Ser Glu Asp Ile Lys Lys Ser Val Leu
355 360 365

Phe Asp Ile Asp Lys Tyr Asn Asp Val Glu Phe Glu Lys Ala Ile Lys

370 375 380

Glu Glu Phe Ile Asn Asn Gly Val Tyr Ile Asn Asn Ile Asp Asn Thr
385 390 395 400

Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His Tyr
405 410 415

Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys Leu
420 425 430

Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe Leu
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Phe Phe Ile Val Asn Ile Thr Gly Gly His Phe Ser Ser Val Leu Ser
450 455 460

Ser Leu Glu Ile Gln Leu Leu Leu Leu Tyr Ile Phe Asn Gln Pro Tyr
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Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys Ile
485 490 495

Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys Gly
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Ile Ser Gly Phe Leu Asn Ile Phe Glu Ser Ile Tyr Asp Lys Phe Gly
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Ala Gly His Ser Ser Thr Ser Leu Ser Ala Ile Gln Gly Tyr Tyr Glu
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Ala Glu Trp Gln Val Lys Asn Lys Glu Lys Tyr Gly Asn Gly Asp Ile
545 550 555 560

Glu Ile Ser Asp Asn Ala Asn Val Thr Asn Asn Glu Arg Ile Phe Gln
565 570 575

Lys Gly Ile His Asn Asp Asn Asn Ile Asn Asn Asn Ile Asn Asn Asn
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Asn Tyr Ile Asn Pro Ser Asp Val Val Gly Arg Glu Asn Thr Asn Val

595 600 605

Pro Asn Val Arg Asn Asp Asn His Asn Val Asp Lys Val His Ile Ala
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Asn Tyr Ile Ser Phe Leu Asn Ser Lys Ile Leu Ile Ile Tyr Asn Asp
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Asn Gly Gln Val Ser Leu Pro Thr Asn Ala Val Ser Ile Ser Gly Asn
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Arg Pro Ile Gly Ser Ile Ser Asp His Leu His Tyr Phe Val Ser Asn
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Ile Glu Ala Asn Ala Gly Asp Asn Lys Leu Ser Lys Asn Ala Lys Glu
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Gly Asn Asn Thr Glu Glu Leu Phe Lys Val Leu Asn Asn Ile Lys Glu
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Asn Asp Phe Ile Asn Ser Lys Ser Pro Ile Ser Ile Leu His Ser Ile
755 760 765

Lys Lys Asn Glu Ile Phe Pro Phe Asp Thr Thr Ile Leu Asn Gly Asn
770 775 780

Ile His Lys Glu Asn Lys Ile Glu Glu Glu Lys Asn Val Ser Ser Ser
785 790 795 800

Thr Lys Tyr Asp Val Asn Asn Lys Asn Asn Lys Asn Asn Asp Asn Ser
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Glu Ile Ile Lys Tyr Glu Asp Met Phe Ser Lys Glu Thr Phe Thr Asp

820 825 830

Ile Tyr Thr Asn Glu Met Leu Lys Tyr Leu Lys Lys Asp Arg Asn Ile
835 840 845

Ile Phe Leu Ser Pro Ala Met Leu Gly Gly Ser Gly Leu Val Lys Ile
850 855 860

Ser Glu Arg Tyr Pro Asn Asn Val Tyr Asp Val Gly Ile Ala Glu Gln
865 870 875 880

His Ser Val Thr Phe Ala Ala Ala Met Ala Met Asn Lys Lys Leu Lys
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Ile Gln Leu Cys Ile Tyr Ser Thr Phe Leu Gln Arg Ala Tyr Asp Gln
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Ile Ile His Asp Leu Asn Leu Gln Asn Ile Pro Leu Lys Val Ile Ile
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Gly Arg Ser Gly Leu Val Gly Glu Asp Gly Ala Thr His Gln Gly Ile
930 935 940

Tyr Asp Leu Ser Tyr Leu Gly Thr Leu Asn Asn Ala Tyr Ile Ile Ser
945 950 955 960

Pro Ser Asn Gln Val Asp Leu Lys Arg Ala Leu Arg Phe Ala Tyr Leu
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Asp Lys Asp His Ser Val Tyr Ile Arg Ile Pro Arg Met Asn Ile Leu
980 985 990

Ser Asp Lys Tyr Met Lys Gly Tyr Leu Asn Ile His Met Lys Asn Glu
995 1000 1005

Ser Lys Asn Ile Asp Val Asn Val Asp Ile Asn Asp Asp Val Asp Lys
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Tyr Ser Glu Glu Tyr Met Asp Asp Asp Asn Phe Ile Lys Ser Phe Ile
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Cys Ile Phe Asn Met Gly Ser Met Leu Phe Asn Val Ile Asn Ala Ile
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Lys Glu Ile Glu Lys Glu Gln Tyr Ile Ser His Asn Tyr Ser Phe Ser
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His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu Asp
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Met Ser Tyr Ile Lys Arg Leu Ile Leu Phe Met
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Ser Asn Val Asn Ile Phe Phe Ala Glu Ala Lys Lys Asn Gly Lys Lys
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Leu Tyr Ser Leu Leu Asn Glu Glu Gly Asn Ser Ser Lys Lys Glu Tyr
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Lys Asn Leu Lys Asp Glu Glu Lys Tyr Asn Ile Ile Gln Asn Ile Lys
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Lys Tyr Cys Glu Cys Thr Lys Lys Tyr Lys Arg Leu Pro Thr Arg Glu
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Gln Ile Arg Lys Cys Lys Asp Leu Gly Ala Asp Ile Val Arg Leu Thr
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Ile Gly Ser Leu Leu Tyr Asp Gly Ile Gly Asp Thr Ile Arg Ile Ser
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Leu Thr Glu Asp Pro Trp Glu Glu Leu Thr Pro Cys Lys Lys Leu Val
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Lys Asn Asn Asn Val Leu His Glu Glu Cys Thr Ile Gly Asn Val Val
    445                 450                 455

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Glu Leu Leu Gln Ser Leu Asn Ile Asn Ile Pro Tyr Ile His Tyr Val
620 625 630 635

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tat gca gga agt tgt ttg atg gat tta atg ggg gat ggt ctt att gtt   2199
Tyr Ala Gly Ser Cys Leu Met Asp Leu Met Gly Asp Gly Leu Ile Val
            655                 660                 665

aac gta act aat gat gtt ctt aca aat aaa aaa aag ata gaa aca aaa   2247
Asn Val Thr Asn Asp Val Leu Thr Asn Lys Lys Lys Ile Glu Thr Lys
        670                 675                 680

tat gat gaa aaa gaa gaa gta gag gaa gag gga aac aat aaa gat att   2295
Tyr Asp Glu Lys Glu Glu Val Glu Glu Glu Gly Asn Asn Lys Asp Ile
    685                 690                 695

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700                 705                 710                 715

att tta caa gat aca aga ata cgt tta ttt aaa aca gat tat ata gcc   2391
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                720                 725                 730

tgc cca tct tgt gga aga act tta ttt aat ata caa gaa act act aaa   2439
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Thr Lys Arg Asn Thr Ile Asn Lys Ser Asp Phe Leu Tyr Ser Leu Leu

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Thr Lys Lys Tyr Lys Arg Leu Pro Thr Arg Glu Val Val Ile Gly Asn
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PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro

INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 7 :
C12N 9/90, 9/10, 9/12, C12Q 1/48

A3

(11) Internationale Veröffentlichungsnummer: WO 00/17233

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(30) Prioritätsdaten:

198 43 279.8	22. September 1998 (22.09.98)	DE
199 23 567.8	21. Mai 1999 (21.05.99)	DE

(71)(72) Anmelder und Erfinder: JOMAA, Hassan [DE/DE]; Breslauer Strasse 24, D-35398 Gießen (DE).

(74) Anwälte: PANTEN, Kirsten usw.; Reichel und Reichel, Parkstrasse 13, D-60322 Frankfurt am Main (DE).

(81) Bestimmungsstaaten: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht
Mit internationalem Recherchenbericht.

(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 25. Mai 2000 (25.05.00)

(54) Title: GENES OF THE 1-DESOXY-D-XYLULOSE BIOSYNTHETIC PATHWAY

(54) Bezeichnung: GENE DES 1-DESOXY-D-XYLULOSE-BIOSYNTHESEWEGS

(57) Abstract

The invention relates to the 1-desoxy- D-xylulose- 5-phosphate reductoisomerase gene, the 1-desoxy- D-xylulose- 5-phosphate-synthase gene and the gcpE gene of the 1-desoxy- D-xylulose biosynthetic pathway and to their use for transforming vectors, host organisms and plants and for determining substances that inhibit this biosynthetic pathway.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft das 1-Desoxy- D-xylulose- 5-phosphatreduktoisomerase -Gen, das 1-Desoxy- D-xylulose-5-phosphat- Synthase- Gen und das gcpE-Gen des 1-Desoxy- D-xylulose- Biosynthesewegs und ihre Verwendung zur Transformation von Vektoren, Wirtsorganismen und Pflanzen und zur Bestimmung von Stoffen, die diesen Biosyntheseweg inhibieren.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AL	Albanien	ES	Spanien	LS	Lesotho	SI	Slowenien
AM	Armenien	FI	Finnland	LT	Litauen	SK	Slowakei
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DE	Deutschland	LI	Liechtenstein	SD	Sudan		
DK	Dänemark	LK	Sri Lanka	SE	Schweden		
EE	Estland	LR	Liberia	SG	Singapur		

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/EP 99/07055

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N9/90 C12N9/10 C12N9/12 C12Q1/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,L	WO 99 52938 A (HASSAN JOMAA) 21 October 1999 (1999-10-21) see SeqID's;Priority of inv. shared by WO9952938 and PCTEP99/07055 and present in DE19816196.4,DE19825585.3,DE19828097.1,DE19831637.2,DE19831639.9 or DE19831638.0 may be invalid; A.4C(4) PC. -/—	1,2,4, 8-12, 16-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2000	23/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoekstra, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUTRA ET AL: "Incorporation of '2,3-'13!C2!- and '2,4-'13!C2!-D-1-Deoxyxylulose into ubiquinone of Escherichia coli via the Mevalonate-Independent pathway for Isoprenoid Biosynthesis" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 39, no. 39, 1998, pages 23-26-26, XP002116676 ISSN: 0040-4039 figure 1	15
X	KUZUYAMA ET AL: "Direct formation of 2-C-Methyl-D-Erythritol 4-phosphate from 1-Deoxy-D-Xylulose 5-phosphate Reductoisomerase, a new enzyme in the non-mevalonate pathway to isopentenyl diphosphate" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 39, no. 39, 1998, pages 4509-4512-44512, XP002116675 ISSN: 0040-4039 figure 1	15
P,X	SCHWENDER, J. ET AL.: "Cloning and heterologous expression of a cDNA encoding 1-deoxy-d-xylulose-5-phosphate reductoisomerase of Arabidopsis thaliana" FEBS LETTERS, vol. 455, July 1999 (1999-07), pages 140-144, XP002132424 the whole document	1,9-12
P,A	DE 197 52 700 A (HOECHST SCHERING AGREVO GMBH) 2 June 1999 (1999-06-02) the whole document	1-12
A	LANGE ET AL: "A family of transketolases that directs isoprenoid biosynthesis via a mevalonate-independent pathway" FASEB JOURNAL,US,FED. OF AMERICAN SOC. FOR EXPERIMENTAL BIOLOGY, BETHESDA, MD, vol. 95, March 1998 (1998-03), pages 2100-2104, XP002116672 ISSN: 0892-6638 the whole document	1-18
P,X	EMINV DATABASE: "AC: EF111813" PLASMODIUM FALCIPARUM 1-DEOXY-D-XYLULOSE 5-PHOSPHATE REDUCTOISOMERASE, 11 January 1999 (1999-01-11), XP002132425 see : Scores	1,9-12

-/—

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	TREMBL DATABASE: "AC: 096693" PLASMODIUM FALCIPARUM 1-DEOXY-D-XYLULOSE 5-PHOSPHATE REDUCTOISOMERASE, 1 May 1999 (1999-05-01), XP002132426 see : Scores	1,9-12
X	SPRENGER ET AL: "Identification of a thiamin-dependent synthase in Escherichia coli required for the formation of the 1-deoxy-D-xylulose 5-phosphate precursor to isoprenoids, thiamin, and pyridoxol" FASEB JOURNAL,US,FED. OF AMERICAN SOC. FOR EXPERIMENTAL BIOLOGY, BETHESDA, MD, vol. 94, November 1997 (1997-11), pages 12857-12862, XP002116674 ISSN: 0892-6638 figure 2	2,9-12
A	figure 1	15
P,X	TREMBL DATABASE: "AC: QZ8HO" CHLAMYDIA PNEUMONIAE GCPE PROTEIN, 1 May 1999 (1999-05-01), XP002132427 see : scores	3,9-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 99/07055

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9952938 A	21-10-1999	DE 19825585 A	21-10-1999
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		DE 19831637 A	27-01-2000
		AU 4120899 A	01-11-1999
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		JP 11169186 A	29-06-1999

INTERNATIONALER RECHERCHENBERICHT

Int. Aktenzeichen
PCT/EP 99/07055

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 C12N9/90 C12N9/10 C12N9/12 C12Q1/48

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 C12N C12Q

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
E,L	WO 99 52938 A (HASSAN JOMAA) 21. Oktober 1999 (1999-10-21) Siehe SeqID's;Priority of inv. shared by WO9952938 and PCTEP99/07055 and present in DE19816196.4,DE19825585.3,DE19828097.1,DE19831637.2,DE19831639.9 or DE19831638.0 may be invalid; A.4C(4) PC. -/---	1,2,4, 8-12, 16-18

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
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"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
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"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
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"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
7. März 2000	23/03/2000

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Hoekstra, S

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	PUTRA ET AL: "Incorporation of '2,3-'13!C2!- and '2,4-'13!C2!-D-1-Deoxyxylulose into ubiquinone of Escherichia coli via the Mevalonate-Independent pathway for Isoprenoid Biosynthesis" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, Bd. 39, Nr. 39, 1998, Seiten 23-26-26, XP002116676 ISSN: 0040-4039 Abbildung 1	15
X	KUZUYAMA ET AL: "Direct formation of 2-C-Methyl-D-Erythritol 4-phosphate from 1-Deoxy-D-Xylulose 5-phosphate Reductoisomerase, a new enzyme in the non-mevalonate pathway to isopentenyl diphosphate" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, Bd. 39, Nr. 39, 1998, Seiten 4509-4512-44512, XP002116675 ISSN: 0040-4039 Abbildung 1	15
P,X	SCHWENDER, J. ET AL.: "Cloning and heterologous expression of a cDNA encoding 1-deoxy-d-xylulose-5-phosphate reductoisomerase of Arabidopsis thaliana" FEBS LETTERS, Bd. 455, Juli 1999 (1999-07), Seiten 140-144, XP002132424 das ganze Dokument	1,9-12
P,A	DE 197 52 700 A (HOECHST SCHERING AGREVO GMBH) 2. Juni 1999 (1999-06-02) das ganze Dokument	1-12
A	LANGE ET AL: "A family of transketolases that directs isoprenoid biosynthesis via a mevalonate-independent pathway" FASEB JOURNAL,US,FED. OF AMERICAN SOC. FOR EXPERIMENTAL BIOLOGY, BETHESDA, MD, Bd. 95, März 1998 (1998-03), Seiten 2100-2104, XP002116672 ISSN: 0892-6638 das ganze Dokument	1-18
P,X	EMINV DATABASE: "AC: EF111813" PLASMODIUM FALCIPARUM 1-DEOXY-D-XYLULOSE 5-PHOSPHATE REDUCTOISOMERASE, 11. Januar 1999 (1999-01-11), XP002132425 Siehe: Scores	1,9-12

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Int. Aktenzeichen
PCT/EP 99/07055

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
P,X	TREMBL DATABASE: "AC: 096693" PLASMODIUM FALCIPARUM 1-DEOXY-D-XYLULOSE 5-PHOSPHATE REDUCTOISOMERASE, 1. Mai 1999 (1999-05-01), XP002132426 Siehe: Scores	1,9-12
X	SPRENGER ET AL: "Identification of a thiamin-dependent synthase in Escherichia coli required for the formation of the 1-deoxy-D-xylulose 5-phosphate precursor to isoprenoids, thiamin, and pyridoxol" FASEB JOURNAL,US,FED. OF AMERICAN SOC. FOR EXPERIMENTAL BIOLOGY, BETHESDA, MD, Bd. 94, November 1997 (1997-11), Seiten 12857-12862, XP002116674 ISSN: 0892-6638	2,9-12
A	Abbildung 2 Abbildung 1	15
P,X	TREMBL DATABASE: "AC: QZ8HO" CHLAMYDIA PNEUMONIAE GCPE PROTEIN, 1. Mai 1999 (1999-05-01), XP002132427 Siehe: scores	3,9-12

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Int. Aktenzeichen
PCT/EP 99/07055

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
WO 9952938 A	21-10-1999	DE 19825585 A	21-10-1999
		DE 19828097 A	30-12-1999
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D O C U M E N T S E R V I C E Order No. 0293339-001

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(54) VOIE DE SYNTHESE BIOLOGIQUE DES GENES DES 1-DESOXY-D-XYLULOSE

(54) GENES OF THE 1-DESOXY-D-XYLULOSE BIOSYNTHETIC PATHWAY

(57) The invention relates to the 1-desoxy- D-xylulose- 5-phosphate reductoisomerase gene, the 1-desoxy- D-xylulose-5-phosphate- synthase gene and the gcpE gene of the 1-desoxy- D-xylulose biosynthetic pathway and to their use for transforming vectors, host organisms and plants and for determining substances that inhibit this biosynthetic pathway.

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(81) Bestimmungsstaaten: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: GENES OF THE 1-DESOXY-D-XYLULOSE BIOSYNTHETIC PATHWAY

(54) Bezeichnung: GENE DES 1-DESOXY-D-XYLULOSE-BIOSYNTHESEWEGS

(57) Abstract

The invention relates to the 1-desoxy- D-xylulose- 5-phosphate reductoisomerase gene, the 1-desoxy- D-xylulose- 5-phosphate-synthase gene and the gcpE gene of the 1-desoxy- D-xylulose biosynthetic pathway and to their use for transforming vectors, host organisms and plants and for determining substances that inhibit this biosynthetic pathway.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft das 1-Desoxy- D-xylulose- 5-phosphatreduktoisomerase -Gen, das 1-Desoxy- D-xylulose-5-phosphat- Synthase- Gen und das gcpE-Gen des 1-Desoxy- D-xylulose- Biosynthesewegs und ihre Verwendung zur Transformation von Vektoren, Wirtsorganismen und Pflanzen und zur Bestimmung von Stoffen, die diesen Biosyntheseweg inhibieren.

Claims

1. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 2 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included.

2. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 4 or for an analogue or derivative of the polypeptide according to SEQ ID no. 4, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included.

3. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 6, in which one or more amino acids have been deleted, added or replaced by other amino acids wherein the catalytic function of the polypeptide is retained.

4. DNA sequence according to one of claims 1 to 3, characterised in that it also comprises functional regulation signals, in particular promoters, operators, enhancers, ribosomal binding sites.

5. DNA sequence with the following sub-sequences
   i) promoter which is active in viruses, eukaryotes and prokaryotes and ensures the formation of an RNA in the intended target tissue or target cells,
   ii) DNA sequences according to one of claims 1 to 3,
   iii) 3' untranslated sequence which, in viruses, eukaryotes and prokaryotes, results in the addition of poly(A) residues onto the 3' end of the RNA.

6. Process for the production of transgenic viruses, eukaryotes and prokaryotes for modifying the isoprenoid content, characterised in that a DNA sequence according to claim 4 or 5 is transferred and incorporated into the genome of viruses, eukaryotic and prokaryotic cells with or without use of a vector.

7. Transgenic systems, in particular plants and plant cells which contain one or more DNA sequences according to claims 1 to 5 as "foreign" or "additional" DNA, which sequences are expressed.

8. Expression vector containing one or more DNA sequences according to claims 1 to 5.

9. Protein which is involved in the 1-deoxy-D-xylulose 5-phosphate metabolic pathway and a) is coded by DNA sequences SEQ ID no. 1, 3 or 5 or b) is coded by DNA sequences which hybridise with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein.

10. Protein according to claim 9, obtainable from the culture supernatants of parasites or from the disrupted parasites and purification by chromatographic and electrophoretic methods.

11. Protein according to one of claims 9 and 10, characterised in that it a) is the product of viral, prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which hybridise with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein, or c) is coded by DNA sequences which would hybridise without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.

12. Protein according to one of the preceding claims, characterised in that it comprises the amino acid sequences SEQ ID no. 2, 4 or 6.

13. Process for determining the enzymatic activity of the gcpE protein, characterised in that phosphorylation of a sugar or of a phosphorus sugar or of a precursor of isoprenoid biosynthesis, in

particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erytritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate, and of phosphate and alcohol precursors, is detected.

14. Process according to claim 13, characterised in that phosphorylation of the following phosphates or alcohols is detected:

$CH_2(OH)-C(CH_3)=C(OH)-CH_2-O-PO(OH)_2$,

$CH_2(OH)-C(CH_3)=C(OH)-CH_2-OH$,

$CH_2(OH)-CH(CH_3)-CO-CH_2-O-PO(OH)_2$,

$CH_2(OH)-CH(CH_3)-CO-CH_2OH$

$CH_2=C(CH_3)-CO-CH_2-O-PO(OH)_2$,

$CH_2=C(CH_3)-CO-CH_2-OH$,

$CH_2=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$,

$CH_2=C(CH_3)-CH(OH)-CH_2-OH$,

$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-O-PO(OH)_2$,

$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-OH$

$CHO-CH(CH_3)-CH(OH)-CH_2-O-PO-(OH)_2$,

$CHO-CH(CH_3)-CH(OH)-CH_2-OH$,

$CH_2(OH)-C(OH)(CH_3)-CH=CH-O-PO(OH)_2$,

$CH_2(OH)-C(OH)(CH_3)-CH=CH-OH$

$CH(OH)=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$,

$CH(OH)=C(CH_3)-CH(OH)-CH_2-OH$,

$(CH_3)_2HC-CO-CH_2-O-PO(OH)_2$,

$(CH_3)_2HC-CO-CH_2-O-H$,

$(CH_3)_2HC-CH(OH)-CH_2-O-PO(OH)_2$,

$(CH_3)_2HC-CH(OH)-CH_2-O-H$.

15. Process for the combined determination of the enzymatic activity of DOXP synthase and of DOXP reductase, characterised in that the conversion of glyceraldehyde 3-phosphate into 2-C-methylerythritol 4-phosphate is detected.

16. Process for screening a compound for the treatment of infectious processes in humans and animals, wherein the process comprises:

a) provision of a host cell which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or analogues thereof, and moreover of a compound suspected to have antimycotic, antibiotic, antiparasitic or antiviral action in humans and animals,

b) bringing the host cell into contact with the compound and

c) determining the antimicrobial, antimycotic, antibiotic, antiparasitic or antiviral action of the compound.

17. Process for screening for compounds for treating plants, wherein the process comprises:

a) provision of a host cell which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or analogues thereof, and moreover of a compound suspected to have antimicrobial,

antiviral, antiparasitic, bactericidal, fungicidal or herbicidal action in plants,

b) bringing the host cell into contact with the compound and

c) determining the antimicrobial, antiviral, antiparasitic, bactericidal, fungicidal or herbicidal action of the compound.

18. Use of DNA according to one of claims 1 to 5 or of proteins according to one of claims 9 to 12 or of transgenic systems according to claim 7 for the prevention or treatment of diseases in humans and animals.

Genes of the 1-deoxy-D-xylulose biosynthesis pathway

The present invention relates to DNA sequences which, when incorporated into the genome of viruses, eukaryotes and prokaryotes, modify isoprenoid biosynthesis and to a genetic engineering process for the production of these transgenic viruses, eukaryotes and prokaryotes. The invention also relates to a process for the identification of substances having herbicidal, antimicrobial, antiparasitic, antiviral, fungicidal, bactericidal action in plants and antimicrobial, antiparasitic, antimycotic, antibacterial and antiviral action in humans and animals.

The biosynthesis pathway for the formation of isoprenoids via the classical acetate/mevalonate pathway and an alternative mevalonate-independent biosynthesis pathway, the deoxy-D-xylulose phosphate pathway is already known (Rohmer, M., Knani, M., Simonin, P., Sutter, B. and Sahm, H. (1993): *Biochem. J.* 295: 517-524).

It is, however, not known how and by which pathways it is possible to bring about a change in the isoprenoid concentration in viruses, eukaryotes and prokaryotes by means of the deoxy-D-xylulose phosphate pathway. Figure 1 shows this biosynthesis pathway.

DNA sequences are consequently provided which code for 1-deoxy-D-xylulase 5-phosphate synthase (DOXP synthase), 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DOXP reductoisomerase) or the gcpE protein. All three genes and enzymes are involved in isoprenoid biosynthesis.

(Translator's comment: The portion at the beginning of the next paragraph enclosed in square brackets corresponds to the beginning of the sentence which finishes on page 2, line 1 of the original).

[The gcpE protein has a kinase function and catalyses the phosphorylation of a sugar or a phosphorus sugar or a precursor of isoprenoid biosynthesis, in particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erytritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose] phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate. In the precursor of isoprenoid synthesis, the gcpE protein in particular catalyses the phosphorylation of the following substances:

$CH_2(OH)-C(CH_3)=C(OH)-CH_2-O-PO(OH)_2$,

$CH_2(OH)-C(CH_3)=C(OH)-CH_2-OH$,

$CH_2(OH)-CH(CH_3)-CO-CH_2-O-PO(OH)_2$,

$CH_2(OH)-CH(CH_3)-CO-CH_2OH$

$CH_2=C(CH_3)-CO-CH_2-O-PO(OH)_2$,

$CH_2=C(CH_3)-CO-CH_2-OH$,

$CH_2=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$,

$CH_2=C(CH_3)-CH(OH)-CH_2-OH$,

$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-O-PO(OH)_2$,

$CH_2(OH)-C(=CH_2)-C(OH)-CH_2-OH$

$CHO-CH(CH_3)-CH(OH)-CH_2-O-PO-(OH)_2$,

$CHO-CH(CH_3)-CH(OH)-CH_2-OH$,

$CH_2(OH)-C(OH)(CH_3)-CH=CH-O-PO(OH)_2$,

$CH_2(OH)-C(OH)(CH_3)-CH=CH-OH$

$CH(OH)=C(CH_3)-CH(OH)-CH_2-O-PO(OH)_2$,

$CH(OH)=C(CH_3)-CH(OH)-CH_2-OH$,

$(CH_3)_2HC-CO-CH_2-O-PO(OH)_2$,

$(CH_3)_2HC-CO-CH_2-O-H$,

$(CH_3)_2HC-CH(OH)-CH_2-O-PO(OH)_2$,

$(CH_3)_2HC-CH(OH)-CH_2-O-H$.

DOXP synthase catalyses the condensation of pyruvate and glyceraldehyde 3-phosphate to yield 1-deoxy-D-xylulose 5-phosphate and DOXP reductoisomerase catalyses the conversion of 1-deoxy-D-xylulose 5-phosphate into 2-C-methyl-D-erythritol 4-phosphate (*c.f.* Fig. 1).

The invention relates to the following DNA sequences:
DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 2 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included,

DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 4 or for an analogue or derivative of the polypeptide according to SEQ ID no. 4, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included,

and DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 6, in which one or more amino acids have been

deleted, added or replaced by other amino acids, wherein the catalytic function of the polypeptide is retained.

The genes and the gene products thereof (polypeptides) are shown with their primary structure and are assigned as follows:

SEQ ID no. 1: 1-deoxy-D-xylulose 5-phosphate reducto-isomerase gene

SEQ ID no. 2: 1-deoxy-D-xylulose 5-phosphate reducto-isomerase

SEQ ID no. 3: 1-deoxy-D-xylulose 5-phosphate synthase gene

SEQ ID no. 4: 1-deoxy-D-xylulose 5-phosphate synthase

SEQ ID no. 5: gcpE gene
SEQ ID no. 6: gcpE proteins.

The DNA sequences all originate from *Plasmodium falciparum*.

Apart from the DNA sequences stated in the sequence listing, suitable sequences are also those which, as a result of the degeneration of the genetic code, have another DNA sequence, but code for the same peptide or for an analogue or derivative of the polypeptide, in which one or more amino acids have been deleted, added or replaced by other amino acids.

The sequences according to the invention are suitable for the expression of genes in viruses, eukaryotes and prokaryotes which are responsible for isoprenoid biosynthesis in the 1-deoxy-D-xylulose pathway.

According to the invention, eukaryotes or eukaryotic cells include animal cells, plant cells, algae, yeasts, fungi, while prokaryotes or prokaryotic cells include bacteria, archaebacteria and eubacteria.

When a DNA sequence is incorporated into a genome on which the above-stated DNA sequence is located, expression of the above-described genes in viruses, eukaryotes and prokaryotes is enabled. The viruses, eukaryotes and prokaryotes transformed according to the invention are cultivated in a manner known *per se* and the isoprenoid formed during such cultivation is isolated and optionally purified. Not all isoprenoids need to be

isolated as in some case the isoprenoids are releas d directly into the ambient air.

The invention furthermore relates to a process for the production of transgenic viruses, eukaryotes and prokaryotes in order to modify the isoprenoid content, which process comprises the following steps.

a) Production of a DNA sequence with the following sub-sequences
   i) promoter which is active in viruses, eukaryotes and prokaryotes and ensures the formation of an RNA in the intended target tissue or target cells,
   ii) DNA sequence which codes for a polypeptide with the amino acid sequence shown in SEQ ID no. 2, 4 or 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, 4 or 6,
   iii) 5' and 3' untranslated sequence which enables or enhances expression of the stated genes in viruses, eukaryotes and prokaryotes,
b) transfer and incorporation of the DNA sequence into the genome of viruses, prokaryotic or eukaryotic cells with or without the use of a vector (for example plasmid, viral DNA).

The intact, whole plants may be regenerated from plant cells transformed in this manner.

The protein-coding sequences with the nucleotide sequences SEQ ID no. 1, SEQ ID no. 3 and SEQ ID no. 5 may be provided with a promoter which ensures transcription in certain organs or cells, which promoter is coupled in

sense orientation (3' end of the promoter to the 5' end of the coding sequence) to the sequence which codes the protein to be formed. A termination signal which determines termination of mRNA synthesis is attached to the 3' end of the coding sequence. In order to direct the protein which is to be expressed to certain subcellular compartments, such as chloroplasts, amyloplasts, mitochondria, vacuoles, cytosol or intercellular spaces, a further sequence which codes for a so-called signal sequence or a transit peptide may be inserted between the promoter and the coding sequence. In some cases, it is necessary to insert sequences which code for a signal at the COOH terminus of the protein. The sequence must be in the same reading frame as the coding sequence of the protein. A large number of cloning vectors is available in order to prepare for the introduction of the DNA sequences according to the invention into higher plants, which vectors contain a replication signal for *E. coli* and a marker which permits selection of the transformed cells. Depending upon the method by which desired genes are introduced into the plant, further DNA sequences may be required. If, for example, the Ti or Ri plasmid is used to transform the plant cells, at least one right border, but frequently the right border and left border of the Ti and Ri plasmid T-DNA must be inserted as a flanking region into the genes to be introduced. The use of T-DNA for transforming plant cells has been intensively investigated and comprehensively described in EP 120516; Hoekama in "The Binary Plant Vector System", Offset-drukkerij Kanters B.V. Alblasserdam (1985), chapter V; Fraley *et al.*, *Crit.Rev.Plant Sci.* 4, 1-46 and An *et al.* (1985) *EMBO J.* 4, 277-287. Once the introduced DNA has been incorporated into the genome, it is

generally stable and is also retained in the descendants of the originally transformed cells. It normally contains a selection marker, which imparts to the transformed plant cells resistance to a biocide or an antibiotic, such as kanamycin, G 418, bleomycin, hygromycin or phosphinotricin and others. The particular marker used is thus intended to allow selection of transformed cells from cells lacking the inserted DNA.

Many techniques are available for introducing DNA into a plant. These techniques include transformation with the assistance of agrobacteria, for example *Agrobacterium tumefaciens*, protoplast fusion, microinjection of DNA, electroporation, as well as ballistic methods and virus infection. Whole plants may then be regenerated from the transformed plant material in a suitable medium which may contain antibiotics or biocides for selection purposes. No particular requirements are placed upon the plasmids for injection and electroporation. However, if whole plants are to be regenerated from such transformed cells, a selectable marker gene must be present. The transformed cells grow in the plants in the conventional manner (McCormick *et al.* (1986), *Plant Cell Reports* 5, 81-84). The plants may be cultivated normally and be crossed with plants which have the same transformed genome or other genomes. The resultant individuals have the corresponding phenotypic properties.

The present invention also provides expression vectors which contain one or more of the DNA sequences according to the invention. Such expression vectors are obtained by providing the DNA sequences according to the invention with suitable functional regulation signals. Such

regulation signals are DNA sequences which are responsible for expression, for example promoters, operators, enhancers, ribosomal binding sites, and are recognised by the host organism.

Further regulation signals, which for example control replication or recombination of the recombinant DNA in the host organism, may optionally also be a constituent part of the expression vector.

The host organisms transformed with the DNA sequences or expression vectors according to the invention are also provided by the present invention.

Suitable host cells and organisms for expressing the enzymes according to the invention are those which comprise no intrinsic enzymes with the function of DOXP synthase, DOXP reductoisomerase or the gcpE protein. This is the case for archaebacteria, animals, fungi, slime moulds and some eubacteria. The absence of such intrinsic enzyme activity substantially facilitates detection and purification of the recombinant enzymes. As a consequence, it is also for the first time possible straightforwardly to measure, in crude extracts from the host cells, the activity and in particular the inhibition of the activity of the recombinant enzymes according to the invention by various chemicals and pharmaceuticals.

The enzymes according to the invention are advantageously then expressed in eukaryotic cells if post-translational modification and native folding of the polypeptide chain is to be achieved. Moreover, depending upon the expression system, it is ensured when expressing genomic

DNA sequences that introns are eliminated by splicing the DNA and the enzymes are produced in the polypeptide sequences characteristic to the parasites. Using recombinant DNA techniques, sequences coding for introns may be eliminated from or inserted for experimental purposes into the DNA sequences to be expressed.

The protein may be isolated from the host cell or the culture supernatant of the host cell using methods known to the person skilled in the art. *In vitro* reactivation of the enzymes may also be required.

In order to facilitate purification, the enzymes according to the invention or sub-sequences of the enzymes may be expressed as fusion proteins with various peptide chains. Oligo-histidine sequences and sequences derived from glutathione S-transferase, thioredoxin or calmodulin-binding peptides are particularly suitable for this purpose.

The enzymes according to the invention or sub-sequences of the enzymes may furthermore be expressed as fusion proteins with such peptide chains known to the person skilled in the art that the recombinant enzymes are transported into the extracellular medium or into certain compartments of the host cells. Both purification and investigation of the biological activity of the enzymes may consequently be facilitated.

When expressing the enzymes according to the invention, it may prove convenient to modify individual codons. Purposeful replacement of bases in the coding region may here also be advisable if the codons used in the

parasites differ from the codon use in the heterologous expression system, in order to ensure optimal synthesis of the protein.

The enzymes according to the invention may furthermore be obtained under standardised conditions by *in vitro* translation by methods known to the person skilled in the art. Systems suitable for this purpose are rabbit reticulocyte and wheat germ extracts and bacterial lysates. *In vitro* transcribed mRNA may also be translated into *Xenopus* oocytes.

Oligo- and polypeptides, the sequences of which are derived from the peptide sequence of the enzymes according to the invention, may be obtained by chemical synthesis. Given appropriate selection of the sequences, such peptides have properties which are characteristic of the enzymes according to the invention. Such peptides may be produced in large quantities and are particularly suitable for investigating the kinetics of enzyme activity, regulation of enzyme activity, the three-dimensional structure of the enzymes, inhibition of enzyme activity by various chemicals and pharmaceuticals and the binding geometry and binding affinity of various ligands.

DNA with the nucleotides from sequences SEQ ID no. 1, 3 and 5 are preferably used for the recombinant production of the enzymes according to the invention.

The invention accordingly moreover relates to a process for screening for compounds which inhibit the deoxy-D-xylulose phosphate metabolic pathway. According to this

process, a host organism, which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or homologues thereof, is provided, as is a compound which is suspected to have antimicrobial, antiparasitic, antibacterial, antiviral and antimycotic action in humans and animals or an antimicrobial, antiviral, bactericidal, herbicidal or fungicidal activity in plants. The host organism is then brought into contact with the compound and the activity of the compound determined.

The present invention also provides methods for determining the enzymatic activity of the gcpE protein. Said activity may be determined using known methods. Determination is performed by detecting the phosphorylation of a sugar or of a phosphorus sugar or of a precursor of isoprenoid biosynthesis, in particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erytritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate. The present invention also provides the use of this measurement method for identifying substances which inhibit the activity of the particular enzymes.

The enzymatic activity of DOXP synthase and DOXP reductoisomerase may be detected in a single step by determining the conversion of glyceraldehyde 3-phosphate into 2-C-methylerythritol 4-phosphate.

Determination of the activities of DOXP synthase and DOXP reductoisomerase proceeds analogously. Fluorimetric methods described by Querol *et al.* are also suitable for determining DOXP synthase activity (Querol *et al.*, abstracts, 4th European Symposium on Plant Isoprenoids, Barcelona, 21-23 April 1999).

SEQUENCE LISTING

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aaa aag gat tta ata gat att ggt gca ata aag aaa cca att aat gta   240
Lys Lys Asp Leu Ile Asp Ile Gly Ala Ile Lys Lys Pro Ile Asn Val
 65                  70                  75                  80

gca att ttt gga agt act ggt agt ata ggt acg aat gct tta aat ata   288
Ala Ile Phe Gly Ser Thr Gly Ser Ile Gly Thr Asn Ala Leu Asn Ile
                85                  90                  95

ata agg gag tgt aat aaa att gaa aat gtt ttt aat gtt aaa gca ttg   336
Ile Arg Glu Cys Asn Lys Ile Glu Asn Val Phe Asn Val Lys Ala Leu
            100                 105                 110

tat gtg aat aag agt gtg aat gaa tta tat gaa caa gct aga gaa ttt   384
Tyr Val Asn Lys Ser Val Asn Glu Leu Tyr Glu Gln Ala Arg Glu Phe
        115                 120                 125

tta cca gaa tat ttg tgt ata cat gat aaa agt gta tat gaa gaa tta   432
Leu Pro Glu Tyr Leu Cys Ile His Asp Lys Ser Val Tyr Glu Glu Leu
    130                 135                 140

aaa gaa ctg gta aaa aat ata aaa gat tat aaa cct ata ata ttg tgt   480
Lys Glu Leu Val Lys Asn Ile Lys Asp Tyr Lys Pro Ile Ile Leu Cys
145                 150                 155                 160

ggt gat gaa ggg atg aaa gaa ata tgt agt agt aat agt ata gat aaa   528
Gly Asp Glu Gly Met Lys Glu Ile Cys Ser Ser Asn Ser Ile Asp Lys
                165                 170                 175

ata gtt att ggt att gat tct ttt caa gga tta tat tct act atg tat   576
Ile Val Ile Gly Ile Asp Ser Phe Gln Gly Leu Tyr Ser Thr Met Tyr
            180                 185                 190

gca att atg aat aat aaa ata gtt gcg tta gct aat aaa gaa tcc att   624
Ala Ile Met Asn Asn Lys Ile Val Ala Leu Ala Asn Lys Glu Ser Ile
        195                 200                 205

gtc tct gct ggt ttc ttt tta aag aaa tta tta aat att cat aaa aat   672
Val Ser Ala Gly Phe Phe Leu Lys Lys Leu Leu Asn Ile His Lys Asn
    210                 215                 220

gca aag ata ata cct gtt gat tca gaa cat agt gct ata ttt caa tgt   720
Ala Lys Ile Ile Pro Val Asp Ser Glu His Ser Ala Ile Phe Gln Cys
225                 230                 235                 240

tta gat aat aat aag gta tta aaa aca aaa tgt tta caa gac aat ttt   768
Leu Asp Asn Asn Lys Val Leu Lys Thr Lys Cys Leu Gln Asp Asn Phe
                245                 250                 255

tct aaa att aac aat ata aat aaa ata ttt tta tgt tca tct gga ggt   816
Ser Lys Ile Asn Asn Ile Asn Lys Ile Phe Leu Cys Ser Ser Gly Gly
            260                 265                 270

cca ttt caa aat tta act atg gac gaa tta aaa aat gta aca tca gaa   864
Pro Phe Gln Asn Leu Thr Met Asp Glu Leu Lys Asn Val Thr Ser Glu
        275                 280                 285
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aat gct tta aag cat cct aaa tgg aaa atg ggt aag aaa ata act ata   912
Asn Ala Leu Lys His Pro Lys Trp Lys Met Gly Lys Lys Ile Thr Ile
    290                 295                 300

gat tct gca act atg atg aat aaa ggt tta gag gtt ata gaa acc cat   960
Asp Ser Ala Thr Met Met Asn Lys Gly Leu Glu Val Ile Glu Thr His
305                 310                 315                 320

ttt tta ttt gat gta gat tat aat gat ata gaa gtt ata gta cat aaa   1008
Phe Leu Phe Asp Val Asp Tyr Asn Asp Ile Glu Val Ile Val His Lys
                325                 330                 335

gaa tgc att ata cat tct tgt gtt gaa ttt ata gac aaa tca gta ata   1056
Glu Cys Ile Ile His Ser Cys Val Glu Phe Ile Asp Lys Ser Val Ile
            340                 345                 350

agt caa atg tat tat cca gat atg caa ata ccc ata tta tat tct tta   1104
Ser Gln Met Tyr Tyr Pro Asp Met Gln Ile Pro Ile Leu Tyr Ser Leu
        355                 360                 365

aca tgg cct gat aga ata aaa aca aat tta aaa cct tta gat ttg gct   1152
Thr Trp Pro Asp Arg Ile Lys Thr Asn Leu Lys Pro Leu Asp Leu Ala
    370                 375                 380

cag gtt tca act ctt aca ttt cat aaa cct tct tta gaa cat ttc ccg   1200
Gln Val Ser Thr Leu Thr Phe His Lys Pro Ser Leu Glu His Phe Pro
385                 390                 395                 400

tgt att aaa tta gct tat caa gca ggt ata aaa gga aac ttt tat cca   1248
Cys Ile Lys Leu Ala Tyr Gln Ala Gly Ile Lys Gly Asn Phe Tyr Pro
            405                 410                 415

act gta cta aat gcg tca aat gaa ata gct aac aac tta ttt ttg aat   1296
Thr Val Leu Asn Ala Ser Asn Glu Ile Ala Asn Asn Leu Phe Leu Asn
        420                 425                 430

aat aaa att aaa tat ttt gat att tcc tct ata ata tcg caa gtt ctt   1344
Asn Lys Ile Lys Tyr Phe Asp Ile Ser Ser Ile Ile Ser Gln Val Leu
    435                 440                 445

gaa tct ttc aat tct caa aag gtt tcg gaa aat agt gaa gat tta atg   1392
Glu Ser Phe Asn Ser Gln Lys Val Ser Glu Asn Ser Glu Asp Leu Met
450                 455                 460

aag caa att cta caa ata cat tct tgg gcc aaa gat aaa gct acc gat   1440
Lys Gln Ile Leu Gln Ile His Ser Trp Ala Lys Asp Lys Ala Thr Asp
465                 470                 475                 480

ata tac aac aaa cat aat tct tca tag                              1467
Ile Tyr Asn Lys His Asn Ser Ser
            485
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<210> 2
<211> 488
<212> PRT
<213> Plasmodium falciparum

<400> 2

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Met Lys Lys Tyr Ile Tyr Ile Tyr Phe Phe Phe Ile Thr Ile Thr Ile
 1               5                  10                  15

Asn Asp Leu Val Ile Asn Asn Thr Ser Lys Cys Val Ser Ile Glu Arg
            20                  25                  30

Arg Lys Asn Asn Ala Tyr Ile Asn Tyr Gly Ile Gly Tyr Asn Gly Pro
        35                  40                  45

Asp Asn Lys Ile Thr Lys Ser Arg Arg Cys Lys Arg Ile Lys Leu Cys
    50                  55                  60

Lys Lys Asp Leu Ile Asp Ile Gly Ala Ile Lys Lys Pro Ile Asn Val
65                  70                  75                  80

Ala Ile Phe Gly Ser Thr Gly Ser Ile Gly Thr Asn Ala Leu Asn Ile
                85                  90                  95

Ile Arg Glu Cys Asn Lys Ile Glu Asn Val Phe Asn Val Lys Ala Leu
            100                 105                 110

Tyr Val Asn Lys Ser Val Asn Glu Leu Tyr Glu Gln Ala Arg Glu Phe
        115                 120                 125

Leu Pro Glu Tyr Leu Cys Ile His Asp Lys Ser Val Tyr Glu Glu Leu
    130                 135                 140

Lys Glu Leu Val Lys Asn Ile Lys Asp Tyr Lys Pro Ile Ile Leu Cys
145                 150                 155                 160

Gly Asp Glu Gly Met Lys Glu Ile Cys Ser Ser Asn Ser Ile Asp Lys
                165                 170                 175

Ile Val Ile Gly Ile Asp Ser Phe Gln Gly Leu Tyr Ser Thr Met Tyr
            180                 185                 190

Ala Ile Met Asn Asn Lys Ile Val Ala Leu Ala Asn Lys Glu Ser Ile
        195                 200                 205

Val Ser Ala Gly Phe Phe Leu Lys Lys Leu Leu Asn Ile His Lys Asn
    210                 215                 220

Ala Lys Ile Ile Pro Val Asp Ser Glu His Ser Ala Ile Phe Gln Cys
225                 230                 235                 240

Leu Asp Asn Asn Lys Val Leu Lys Thr Lys Cys Leu Gln Asp Asn Phe
                245                 250                 255

Ser Lys Ile Asn Asn Ile Asn Lys Ile Phe Leu Cys Ser Ser Gly Gly
            260                 265                 270

Pro Phe Gln Asn Leu Thr Met Asp Glu Leu Lys Asn Val Thr Ser Glu
        275                 280                 285

Asn Ala Leu Lys His Pro Lys Trp Lys Met Gly Lys Lys Ile Thr Ile
    290                 295                 300
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Asp S r Ala Thr Met Met Asn Lys Gly Leu Glu Val Ile Glu Thr His
305                 310                 315                 320

Phe Leu Phe Asp Val Asp Tyr Asn Asp Ile Glu Val Ile Val His Lys
                325                 330                 335

Glu Cys Ile Ile His Ser Cys Val Glu Phe Ile Asp Lys Ser Val Ile
            340                 345                 350

Ser Gln Met Tyr Tyr Pro Asp Met Gln Ile Pro Ile Leu Tyr Ser Leu
        355                 360                 365

Thr Trp Pro Asp Arg Ile Lys Thr Asn Leu Lys Pro Leu Asp Leu Ala
    370                 375                 380

Gln Val Ser Thr Leu Thr Phe His Lys Pro Ser Leu Glu His Phe Pro
385                 390                 395                 400

Cys Ile Lys Leu Ala Tyr Gln Ala Gly Ile Lys Gly Asn Phe Tyr Pro
                405                 410                 415

Thr Val Leu Asn Ala Ser Asn Glu Ile Ala Asn Asn Leu Phe Leu Asn
            420                 425                 430

Asn Lys Ile Lys Tyr Phe Asp Ile Ser Ser Ile Ile Ser Gln Val Leu
        435                 440                 445

Glu Ser Phe Asn Ser Gln Lys Val Ser Glu Asn Ser Glu Asp Leu Met
    450                 455                 460

Lys Gln Ile Leu Gln Ile His Ser Trp Ala Lys Asp Lys Ala Thr Asp
465                 470                 475                 480

Ile Tyr Asn Lys His Asn Ser Ser .
                485
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<210> 3
<211> 3872
<212> DNA
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<220>
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aataatattc taaatttacc ttccgttttt gctcgatctt ctcatttcg tttcagcttt 120

tatca atg att ttt aat tat gtg ttt ttt aag aac ttt gta cca gtt gtt 170
      Met Ile Phe Asn Tyr Val Phe Phe Lys Asn Phe Val Pro Val Val
        1               5                  10                  15

cta tac att ctc ctt ata ata tat att aac tta aat ggc atg aat aat   218
L u Tyr Ile Leu Leu Ile Ile Tyr Ile Asn Leu Asn Gly Met Asn Asn
                  20                  25                  30

aaa aat caa ata aaa aca gaa aaa att tat ata aag aaa ttg aat agg   266
Lys Asn Gln Ile Lys Thr Glu Lys Ile Tyr Ile Lys Lys Leu Asn Arg
             35                  40                  45

ttg tca agg aaa aat tcg tta tgt agt tct aaa aat aaa ata gca tgc   314
Leu Ser Arg Lys Asn Ser Leu Cys Ser Ser Lys Asn Lys Ile Ala Cys
         50                  55                  60

ttg ttc gat ata gga aat gat gat aat aga aat acg aca tat ggc tat   362
Leu Phe Asp Ile Gly Asn Asp Asp Asn Arg Asn Thr Thr Tyr Gly Tyr
     65                  70                  75

aat gtg aat gtt aaa aat gat gat att aat tcc tta cta aaa aat aat   410
Asn Val Asn Val Lys Asn Asp Asp Ile Asn Ser Leu Leu Lys Asn Asn
 80                  85                  90                  95

tat agt aat aaa ttg tac atg gat aag agg aaa aat att aat aat gta   458
Tyr Ser Asn Lys Leu Tyr Met Asp Lys Arg Lys Asn Ile Asn Asn Val
                100                 105                 110

att agt act aat aaa ata tct ggg tcc att tca aat att tgt agt aga   506
Il  Ser Thr Asn Lys Ile Ser Gly Ser Ile Ser Asn Ile Cys Ser Arg
            115                 120                 125

aat caa aaa gaa aat gaa caa aaa aga aat aaa caa aga tgt tta act   554
Asn Gln Lys Glu Asn Glu Gln Lys Arg Asn Lys Gln Arg Cys Leu Thr
        130                 135                 140

caa tgt cac act tat aat atg tca cat gaa cag gac aaa cta gct aat   602
Gln Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn
    145                 150                 155

gat aat aat agg aat aat aaa aag aat ttt aat tta tta ttt ata aat   650
Asp Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn
160                 165                 170                 175

tat ttt aat ttg aaa cga atg aaa aat tct ctt cta aat aaa gac aat   698
Tyr Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn
                180                 185                 190

ttc ttt tac tgt aaa gaa aaa aaa ttg tca ttt ctg cat aag gcc tat   746
Phe Phe Tyr Cys Lys Glu Lys Lys Leu Ser Phe Leu His Lys Ala Tyr
            195                 200                 205

aaa aaa aaa aat tgc act ttt caa aat tat agt tta aaa aga aaa tct   794
Lys Lys Lys Asn Cys Thr Phe Gln Asn Tyr Ser Leu Lys Arg Lys Ser
        210                 215                 220
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aat cgt gat tca cat aaa ttg ttt tct gga gaa ttt gac gat tat aca   842
Asn Arg Asp Ser His Lys Leu Phe Ser Gly Glu Phe Asp Asp Tyr Thr
    225                 230                 235

aat aat aat gct tta tat gaa tcc gaa aaa aaa gaa tac att aca cta   890
Asn Asn Asn Ala Leu Tyr Glu Ser Glu Lys Lys Glu Tyr Ile Thr Leu
240                 245                 250                 255

aat aat aat aat aaa aat aat aat aat aaa aat aat gat aat aaa aat   938
Asn Asn Asn Asn Lys Asn Asn Asn Asn Lys Asn Asn Asp Asn Lys Asn
                260                 265                 270

aat gat aat aat gat tat aat aat aat aat agt tgt aat aat tta gga   986
Asn Asp Asn Asn Asp Tyr Asn Asn Asn Asn Ser Cys Asn Asn Leu Gly
            275                 280                 285

gag aga tcc aat cat tat gat aat tat ggt gga gat aat aat aat cca   1034
Glu Arg Ser Asn His Tyr Asp Asn Tyr Gly Gly Asp Asn Asn Asn Pro
        290                 295                 300

tgt aat aat aat aat gac aaa tat gat ata gga aaa tat ttc aaa cag   1082
Cys Asn Asn Asn Asn Asp Lys Tyr Asp Ile Gly Lys Tyr Phe Lys Gln
    305                 310                 315

att aat acc ttt att aat att gat gaa tat aaa act ata tat ggt gat   1130
Ile Asn Thr Phe Ile Asn Ile Asp Glu Tyr Lys Thr Ile Tyr Gly Asp
320                 325                 330                 335

gaa ata tat aaa gaa ata tat gaa cta tat gta gaa aga aat att cct   1178
Glu Ile Tyr Lys Glu Ile Tyr Glu Leu Tyr Val Glu Arg Asn Ile Pro
                340                 345                 350

gaa tat tat gaa cga aaa tat ttt tca gaa gat att aaa aag agt gtc   1226
Glu Tyr Tyr Glu Arg Lys Tyr Phe Ser Glu Asp Ile Lys Lys Ser Val
            355                 360                 365

cta ttt gat ata gat aaa tat aat gat gtc gaa ttt gaa aaa gct ata   1274
Leu Phe Asp Ile Asp Lys Tyr Asn Asp Val Glu Phe Glu Lys Ala Ile
        370                 375                 380

aaa gaa gaa ttt ata aat aat gga gtt tat att aat aat ata gat aat   1322
Lys Glu Glu Phe Ile Asn Asn Gly Val Tyr Ile Asn Asn Ile Asp Asn
    385                 390                 395

aca tat tat aaa aaa gaa aat att tta ata atg aaa aag ata tta cat   1370
Thr Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His
400                 405                 410                 415

tat ttc cca tta tta aaa tta att aat aat cca tca gat tta aaa aag   1418
Tyr Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys
                420                 425                 430

tta aaa aaa caa tat tta cct tta tta gca cat gaa tta aaa ata ttt   1466
Leu Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe
            435                 440                 445
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tta ttt ttt att gta aat ata aca gga ggt cat ttt tcc tct gtt tta   1514
Leu Phe Ph  Ile Val Asn Ile Thr Gly Gly His Phe Ser Ser Val Leu
        450                 455                 460

agc tct tta gaa att caa tta tta tta ttg tat att ttt aat caa cca   1562
Ser Ser Leu Glu Ile Gln Leu Leu Leu Leu Tyr Ile Phe Asn Gln Pro
    465                 470                 475

tat gat aat gtt ata tat gat ata gga cat caa gca tat gta cat aag   1610
Tyr Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys
480                 485                 490                 495

ata ttg acc gga aga aaa cta tta ttt cta tca tta aga aat aaa aaa   1658
Ile Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys
                500                 505                 510

ggt att agt gga ttc cta aat att ttt gaa agt att tat gat aaa ttt   1706
Gly Ile Ser Gly Phe Leu Asn Ile Phe Glu Ser Ile Tyr Asp Lys Phe
            515                 520                 525

ggg gct ggt cac agt tcc act tca tta agt gct ata caa gga tat tat   1754
Gly Ala Gly His Ser Ser Thr Ser Leu Ser Ala Ile Gln Gly Tyr Tyr
        530                 535                 540

gaa gcc gag tgg caa gtg aag aat aaa gaa aaa tat gga aat gga gat   1802
Glu Ala Glu Trp Gln Val Lys Asn Lys Glu Lys Tyr Gly Asn Gly Asp
    545                 550                 555

ata gaa ata agt gat aac gca aat gtc acg aat aat gaa agg ata ttt   1850
Ile Glu Ile Ser Asp Asn Ala Asn Val Thr Asn Asn Glu Arg Ile Phe
560                 565                 570                 575

caa aaa gga ata cac aat gat aat aat att aac aat aat att aat aat   1898
Gln Lys Gly Ile His Asn Asp Asn Asn Ile Asn Asn Asn Ile Asn Asn
                580                 585                 590

aat aat tat atc aat cct tca gat gtg gta gga aga gaa aat acg aat   1946
Asn Asn Tyr Ile Asn Pro Ser Asp Val Val Gly Arg Glu Asn Thr Asn
            595                 600                 605

gta cca aat gta cga aat gat aac cat aac gtg gat aaa gta cac att   1994
Val Pro Asn Val Arg Asn Asp Asn His Asn Val Asp Lys Val His Ile
        610                 615                 620

gct att ata gga gat ggt ggt tta aca ggt gga atg gca tta gaa gcg   2042
Ala Ile Ile Gly Asp Gly Gly Leu Thr Gly Gly Met Ala Leu Glu Ala
    625                 630                 635

tta aat tat att tca ttc ttg aat tct aaa att tta att att tat aat   2090
Leu Asn Tyr Ile Ser Phe Leu Asn Ser Lys Ile Leu Ile Ile Tyr Asn
640                 645                 650                 655

gat aac gga caa gtt tct tta cca aca aat gcc gta agt ata tca ggt   2138
Asp Asn Gly Gln Val Ser Leu Pro Thr Asn Ala Val Ser Ile Ser Gly
                660                 665                 670
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aat aga cct ata ggt tct ata tca gat cat tta cat tat ttt gtt tct   2186
Asn Arg Pro Ile Gly Ser Ile Ser Asp His Leu His Tyr Phe Val Ser
            675                 680                 685

aat ata gaa gca aat gct ggt gat aat aaa tta tcg aaa aat gca aaa   2234
Asn Ile Glu Ala Asn Ala Gly Asp Asn Lys Leu Ser Lys Asn Ala Lys
        690                 695                 700

gag aat aac att ttt gaa aat ttg aat tat gat tat att ggt gtt gtg   2282
Glu Asn Asn Ile Phe Glu Asn Leu Asn Tyr Asp Tyr Ile Gly Val Val
    705                 710                 715

aat ggt aat aat aca gaa gag ctc ttt aaa gta tta aat aat ata aaa   2330
Asn Gly Asn Asn Thr Glu Glu Leu Phe Lys Val Leu Asn Asn Ile Lys
720                 725                 730                 735

gaa aat aaa tta aaa aga gct act gtt ctt cat gta cgt aca aaa aaa   2378
Glu Asn Lys Leu Lys Arg Ala Thr Val Leu His Val Arg Thr Lys Lys
                740                 745                 750

tcg aat gat ttt ata aat tca aag agt cca ata agt ata ttg cac tct   2426
Ser Asn Asp Phe Ile Asn Ser Lys Ser Pro Ile Ser Ile Leu His Ser
            755                 760                 765

ata aag aaa aat gag att ttc cct ttc gat acc act ata tta aat gga   2474
Ile Lys Lys Asn Glu Ile Phe Pro Phe Asp Thr Thr Ile Leu Asn Gly
        770                 775                 780

aat att cat aag gag aac aag ata gaa gaa gag aaa aat gtg tct tca   2522
Asn Ile His Lys Glu Asn Lys Ile Glu Glu Glu Lys Asn Val Ser Ser
    785                 790                 795

tct aca aag tat gat gta aat aat aag aat aat aaa aat aat gat aat   2570
Ser Thr Lys Tyr Asp Val Asn Asn Lys Asn Asn Lys Asn Asn Asp Asn
800                 805                 810                 815

agt gaa att ata aaa tat gaa gat atg ttt tca aaa gag acg ttc aca   2618
Ser Glu Ile Ile Lys Tyr Glu Asp Met Phe Ser Lys Glu Thr Phe Thr
                820                 825                 830

gat ata tat aca aat gaa atg tta aaa tat tta aag aaa gat aga aat   2666
Asp Ile Tyr Thr Asn Glu Met Leu Lys Tyr Leu Lys Lys Asp Arg Asn
            835                 840                 845

ata ata ttc cta tct ccc gct atg tta gga gga tca gga ttg gtt aaa   2714
Ile Ile Phe Leu Ser Pro Ala Met Leu Gly Gly Ser Gly Leu Val Lys
        850                 855                 860

att agt gag cgt tat cca aat aat gta tat gat gta ggt ata gca gaa   2762
Ile Ser Glu Arg Tyr Pro Asn Asn Val Tyr Asp Val Gly Ile Ala Glu
    865                 870                 875

caa cat tct gta act ttc gca gca gct atg gca atg aat aag aaa tta   2810
Gln His Ser Val Thr Phe Ala Ala Ala Met Ala Met Asn Lys Lys Leu
880                 885                 890                 895
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aaa ata caa tta tgt ata tat tcg acc ttt tta caa aga gca tat gat   2858
Lys Ile Gln Leu Cys Ile Tyr Ser Thr Phe Leu Gln Arg Ala Tyr Asp
                900                 905                 910

caa att ata cat gat ctt aat tta caa aat ata cct tta aag gtt ata   2906
Gln Ile Ile His Asp Leu Asn Leu Gln Asn Ile Pro Leu Lys Val Ile
            915                 920                 925

att gga aga agt gga tta gta gga gag gat ggg gca aca cat caa ggt   2954
Ile Gly Arg Ser Gly Leu Val Gly Glu Asp Gly Ala Thr His Gln Gly
        930                 935                 940

ata tat gat tta tct tat ctt ggg aca ctt aac aat gca tat ata ata   3002
Ile Tyr Asp Leu Ser Tyr Leu Gly Thr Leu Asn Asn Ala Tyr Ile Ile
    945                 950                 955

tct cca agt aat caa gtt gat ttg aaa aga gct ctt agg ttt gct tat   3050
Ser Pro Ser Asn Gln Val Asp Leu Lys Arg Ala Leu Arg Phe Ala Tyr
960                 965                 970                 975

tta gat aag gac cat tct gtg tat ata cgt ata ccc aga atg aac ata   3098
Leu Asp Lys Asp His Ser Val Tyr Ile Arg Ile Pro Arg Met Asn Ile
                980                 985                 990

tta agt gat aag tac atg aaa gga tat ttg aac att cat atg aaa aat   3146
L u Ser Asp Lys Tyr Met Lys Gly Tyr Leu Asn Ile His Met Lys Asn
            995                1000                1005

gag agc aaa aat atc gat gta aac gtg gat ata aac gat gat gta gat   3194
Glu Ser Lys Asn Ile Asp Val Asn Val Asp Ile Asn Asp Asp Val Asp
        1010                1015                1020

aaa tat agt gaa gaa tat atg gac gat gat aat ttt ata aaa tcg ttt   3242
Lys Tyr Ser Glu Glu Tyr Met Asp Asp Asp Asn Phe Ile Lys Ser Phe
    1025                1030                1035

att gga aaa tct aga att att aaa atg gat aat gaa aat aat aat aca   3290
Ile Gly Lys Ser Arg Ile Ile Lys Met Asp Asn Glu Asn Asn Asn Thr
1040                1045                1050                1055

aat gaa cat tat tca agc aga gga gat aca cag aca aaa aaa aaa aaa   3338
Asn Glu His Tyr Ser Ser Arg Gly Asp Thr Gln Thr Lys Lys Lys Lys
                1060                1065                1070

gtt tgt atc ttt aac atg ggt agt atg ctt ttt aat gta att aat gct   3386
Val Cys Ile Phe Asn Met Gly Ser Met Leu Phe Asn Val Ile Asn Ala
            1075                1080                1085

ata aaa gaa att gaa aaa gaa caa tat att tca cat aat tat tct ttt   3434
Ile Lys Glu Ile Glu Lys Glu Gln Tyr Ile Ser His Asn Tyr Ser Phe
        1090                1095                1100

tca att gtt gat atg ata ttt tta aat cct tta gat aaa aat atg ata   3482
Ser Ile Val Asp Met Ile Phe Leu Asn Pro Leu Asp Lys Asn Met Ile
    1105                1110                1115
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gat cat gta ata aaa caa aat aaa cat caa tat tta att act tat gaa   3530
Asp His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu
1120                1125                1130                1135

gat aat act ata ggt ggt ttt tct aca cat ttc aat aat tat tta ata   3578
Asp Asn Thr Ile Gly Gly Phe Ser Thr His Phe Asn Asn Tyr Leu Ile
                1140                1145                1150

gaa aat aat tat att aca aaa cat aac tta tat gtt cat aat att tat   3626
Glu Asn Asn Tyr Ile Thr Lys His Asn Leu Tyr Val His Asn Ile Tyr
            1155                1160                1165

tta tct aat gag cca att gaa cat gca tct ttt aag gat caa caa gaa   3674
Leu Ser Asn Glu Pro Ile Glu His Ala Ser Phe Lys Asp Gln Gln Glu
        1170                1175                1180

gtc gtc aaa atg gat aaa tgt agt ctt gtc aat aga att aaa aat tat   3722
Val Val Lys Met Asp Lys Cys Ser Leu Val Asn Arg Ile Lys Asn Tyr
    1185                1190                1195

ctt aaa aat aat cct aca tgatgtaaga taaatatata tttctaaaat          3770
Leu Lys Asn Asn Pro Thr
1200                1205

tatttttttt ttatacttta atgtgtacaa taaaatatat atctaaatat attttatttg 3830

tacgcttttt ttttttttt tttaattgtt atttttgtat at                     3872
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<213> Plasmodium falciparum

<400> 4

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Tyr Ile Leu Leu Ile Ile Tyr Ile Asn Leu Asn Gly Met Asn Asn Lys
             20                  25                  30

Asn Gln Ile Lys Thr Glu Lys Ile Tyr Ile Lys Lys Leu Asn Arg Leu
         35                  40                  45

Ser Arg Lys Asn Ser Leu Cys Ser Ser Lys Asn Lys Ile Ala Cys Leu
     50                  55                  60

Phe Asp Ile Gly Asn Asp Asp Asn Arg Asn Thr Thr Tyr Gly Tyr Asn
 65                  70                  75                  80

Val Asn Val Lys Asn Asp Asp Ile Asn Ser Leu Leu Lys Asn Asn Tyr
                 85                  90                  95

Ser Asn Lys Leu Tyr Met Asp Lys Arg Lys Asn Ile Asn Asn Val Ile
            100                 105                 110

Ser Thr Asn Lys Ile Ser Gly Ser Ile Ser Asn Ile Cys Ser Arg Asn
        115                 120                 125
```

```
Gln Lys Glu Asn Glu Gln Lys Arg Asn Lys Gln Arg Cys Leu Thr Gln
    130                 135                 140

Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn Asp
145                 150                 155                 160

Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn Tyr
                165                 170                 175

Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn Phe
            180                 185                 190

Phe Tyr Cys Lys Glu Lys Lys Leu Ser Phe Leu His Lys Ala Tyr Lys
        195                 200                 205

Lys Lys Asn Cys Thr Phe Gln Asn Tyr Ser Leu Lys Arg Lys Ser Asn
    210                 215                 220

Arg Asp Ser His Lys Leu Phe Ser Gly Glu Phe Asp Asp Tyr Thr Asn
225                 230                 235                 240

Asn Asn Ala Leu Tyr Glu Ser Glu Lys Lys Glu Tyr Ile Thr Leu Asn
                245                 250                 255

Asn Asn Asn Lys Asn Asn Asn Asn Lys Asn Asn Asp Asn Lys Asn Asn
            260                 265                 270

Asp Asn Asn Asp Tyr Asn Asn Asn Asn Ser Cys Asn Asn Leu Gly Glu
        275                 280                 285

Arg Ser Asn His Tyr Asp Asn Tyr Gly Gly Asp Asn Asn Asn Pro Cys
    290                 295                 300

Asn Asn Asn Asn Asp Lys Tyr Asp Ile Gly Lys Tyr Phe Lys Gln Ile
305                 310                 315                 320

Asn Thr Phe Ile Asn Ile Asp Glu Tyr Lys Thr Ile Tyr Gly Asp Glu
                325                 330                 335

Ile Tyr Lys Glu Ile Tyr Glu Leu Tyr Val Glu Arg Asn Ile Pro Glu
            340                 345                 350

Tyr Tyr Glu Arg Lys Tyr Phe Ser Glu Asp Ile Lys Lys Ser Val Leu
        355                 360                 365

Phe Asp Ile Asp Lys Tyr Asn Asp Val Glu Phe Glu Lys Ala Ile Lys
    370                 375                 380

Glu Glu Phe Ile Asn Asn Gly Val Tyr Ile Asn Asn Ile Asp Asn Thr
385                 390                 395                 400

Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His Tyr
                405                 410                 415

Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys Leu
            420                 425                 430
```

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Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe Leu
        435                 440                 445

Phe Phe Ile Val Asn Ile Thr Gly Gly His Phe Ser Ser Val Leu Ser
    450                 455                 460

Ser Leu Glu Ile Gln Leu Leu Leu Leu Tyr Ile Phe Asn Gln Pro Tyr
465                 470                 475                 480

Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys Ile
                485                 490                 495

Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys Gly
            500                 505                 510

Ile Ser Gly Phe Leu Asn Ile Phe Glu Ser Ile Tyr Asp Lys Phe Gly
        515                 520                 525

Ala Gly His Ser Ser Thr Ser Leu Ser Ala Ile Gln Gly Tyr Tyr Glu
    530                 535                 540

Ala Glu Trp Gln Val Lys Asn Lys Glu Lys Tyr Gly Asn Gly Asp Ile
545                 550                 555                 560

Glu Ile Ser Asp Asn Ala Asn Val Thr Asn Asn Glu Arg Ile Phe Gln
                565                 570                 575

Lys Gly Ile His Asn Asp Asn Asn Ile Asn Asn Asn Ile Asn Asn Asn
            580                 585                 590

Asn Tyr Ile Asn Pro Ser Asp Val Val Gly Arg Glu Asn Thr Asn Val
        595                 600                 605

Pro Asn Val Arg Asn Asp Asn His Asn Val Asp Lys Val His Ile Ala
    610                 615                 620

Ile Ile Gly Asp Gly Gly Leu Thr Gly Gly Met Ala Leu Glu Ala Leu
625                 630                 635                 640

Asn Tyr Ile Ser Phe Leu Asn Ser Lys Ile Leu Ile Ile Tyr Asn Asp
                645                 650                 655

Asn Gly Gln Val Ser Leu Pro Thr Asn Ala Val Ser Ile Ser Gly Asn
            660                 665                 670

Arg Pro Ile Gly Ser Ile Ser Asp His Leu His Tyr Phe Val Ser Asn
        675                 680                 685

Ile Glu Ala Asn Ala Gly Asp Asn Lys Leu Ser Lys Asn Ala Lys Glu
    690                 695                 700

Asn Asn Ile Phe Glu Asn Leu Asn Tyr Asp Tyr Ile Gly Val Val Asn
705                 710                 715                 720

Gly Asn Asn Thr Glu Glu Leu Phe Lys Val Leu Asn Asn Ile Lys Glu
                725                 730                 735
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Asn Lys Leu Lys Arg Ala Thr Val Leu His Val Arg Thr Lys Lys S r
            740                 745                 750

Asn Asp Phe Ile Asn Ser Lys Ser Pro Ile Ser Ile Leu His Ser Ile
        755                 760                 765

Lys Lys Asn Glu Ile Phe Pro Phe Asp Thr Thr Ile Leu Asn Gly Asn
    770                 775                 780

Ile His Lys Glu Asn Lys Ile Glu Glu Glu Lys Asn Val Ser Ser Ser
785                 790                 795                 800

Thr Lys Tyr Asp Val Asn Asn Lys Asn Asn Lys Asn Asn Asp Asn Ser
                805                 810                 815

Glu Ile Ile Lys Tyr Glu Asp Met Phe Ser Lys Glu Thr Phe Thr Asp
            820                 825                 830

Ile Tyr Thr Asn Glu Met Leu Lys Tyr Leu Lys Lys Asp Arg Asn Ile
        835                 840                 845

Ile Phe Leu Ser Pro Ala Met Leu Gly Gly Ser Gly Leu Val Lys Ile
    850                 855                 860

Ser Glu Arg Tyr Pro Asn Asn Val Tyr Asp Val Gly Ile Ala Glu Gln
865                 870                 875                 880

His Ser Val Thr Phe Ala Ala Ala Met Ala Met Asn Lys Lys Leu Lys
                885                 890                 895

Ile Gln Leu Cys Ile Tyr Ser Thr Phe Leu Gln Arg Ala Tyr Asp Gln
            900                 905                 910

Ile Ile His Asp Leu Asn Leu Gln Asn Ile Pro Leu Lys Val Ile Ile
        915                 920                 925

Gly Arg Ser Gly Leu Val Gly Glu Asp Gly Ala Thr His Gln Gly Ile
    930                 935                 940

Tyr Asp Leu Ser Tyr Leu Gly Thr Leu Asn Asn Ala Tyr Ile Ile Ser
945                 950                 955                 960

Pro Ser Asn Gln Val Asp Leu Lys Arg Ala Leu Arg Phe Ala Tyr Leu
                965                 970                 975

Asp Lys Asp His Ser Val Tyr Ile Arg Ile Pro Arg Met Asn Ile Leu
            980                 985                 990

Ser Asp Lys Tyr Met Lys Gly Tyr Leu Asn Ile His Met Lys Asn Glu
        995                1000                1005

Ser Lys Asn Ile Asp Val Asn Val Asp Ile Asn Asp Asp Val Asp Lys
   1010                1015                1020

Tyr Ser Glu Glu Tyr Met Asp Asp Asp Asn Phe Ile Lys Ser Phe Ile
025                1030                1035                1040
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Gly Lys Ser Arg Ile Ile Lys Met Asp Asn Glu Asn Asn Asn Thr Asn
1045 1050 1055

Glu His Tyr Ser Ser Arg Gly Asp Thr Gln Thr Lys Lys Lys Lys Val
1060 1065 1070

Cys Ile Phe Asn Met Gly Ser Met Leu Phe Asn Val Ile Asn Ala Ile
1075 1080 1085

Lys Glu Ile Glu Lys Glu Gln Tyr Ile Ser His Asn Tyr Ser Phe Ser
1090 1095 1100

Ile Val Asp Met Ile Phe Leu Asn Pro Leu Asp Lys Asn Met Ile Asp
105 1110 1115 1120

His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu Asp
1125 1130 1135

Asn Thr Ile Gly Gly Phe Ser Thr His Phe Asn Asn Tyr Leu Ile Glu
1140 1145 1150

Asn Asn Tyr Ile Thr Lys His Asn Leu Tyr Val His Asn Ile Tyr Leu
1155 1160 1165

Ser Asn Glu Pro Ile Glu His Ala Ser Phe Lys Asp Gln Gln Glu Val
1170 1175 1180

Val Lys Met Asp Lys Cys Ser Leu Val Asn Arg Ile Lys Asn Tyr Leu
185 1190 1195 1200

Lys Asn Asn Pro Thr
1205

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<220>
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atacatctcc aacatataaa tattattttt tattattatt ttttttttt tttttcataa 180

tgcctgaata accacaaa atg agt tat ata aaa aga ctg att ctt ttt atg 231
Met Ser Tyr Ile Lys Arg Leu Ile Leu Phe Met
1 5 10

tta ctg ttt tat tct cat gta aaa att aaa aaa tta ttt att aaa att 279
L u Leu Ph Tyr Ser His Val Lys Ile Lys Lys Leu Ph Ile Lys Ile
15 20 25

```
tct aat gta aac ata ttt ttt gca gaa gca aag aaa aat gga aaa aag   327
Ser Asn Val Asn Ile Phe Phe Ala Glu Ala Lys Lys Asn Gly Lys Lys
         30                  35                  40

gaa ttc ttt ctt ttt tta cta aat ata aaa aaa aat agc caa cag aaa   375
Glu Phe Phe Leu Phe Leu Leu Asn Ile Lys Lys Asn Ser Gln Gln Lys
     45                  50                  55

aaa act tat cat att acc aaa agg aat acc ata aat aaa agt gat ttt   423
Lys Thr Tyr His Ile Thr Lys Arg Asn Thr Ile Asn Lys Ser Asp Phe
 60                  65                  70                  75

tta tat tct tta cta aat gaa gaa ggg aat tct tca aaa aag gaa tat   471
Leu Tyr Ser Leu Leu Asn Glu Glu Gly Asn Ser Ser Lys Lys Glu Tyr
                 80                  85                  90

aaa aat tta aaa gat gaa gaa aaa tat aat atc ata caa aat ata aaa   519
Lys Asn Leu Lys Asp Glu Glu Lys Tyr Asn Ile Ile Gln Asn Ile Lys
            95                 100                 105

aaa tat tgt gaa tgt act aaa aaa tat aaa agg ctc cca aca cga gaa   567
Lys Tyr Cys Glu Cys Thr Lys Lys Tyr Lys Arg Leu Pro Thr Arg Glu
        110                 115                 120

gta gtt att gga aat gtt aaa att gga gga aat aat aaa ata gct att   615
Val Val Ile Gly Asn Val Lys Ile Gly Gly Asn Asn Lys Ile Ala Ile
    125                 130                 135

caa act atg gct agc tgt gat aca aga aat gta gaa gaa tgt gta tat   663
Gln Thr Met Ala Ser Cys Asp Thr Arg Asn Val Glu Glu Cys Val Tyr
140                 145                 150                 155

caa att aga aaa tgt aaa gat ttg ggt gct gac att gta agg ttg act   711
Gln Ile Arg Lys Cys Lys Asp Leu Gly Ala Asp Ile Val Arg Leu Thr
                160                 165                 170

gtt caa gga gtt caa gaa gca caa gct agt tat cat att aaa gaa aaa   759
Val Gln Gly Val Gln Glu Ala Gln Ala Ser Tyr His Ile Lys Glu Lys
            175                 180                 185

tta tta tct gaa aat gta aat atc cca tta gta gca gat att cat ttt   807
Leu Leu Ser Glu Asn Val Asn Ile Pro Leu Val Ala Asp Ile His Phe
        190                 195                 200

aat cct aaa ata gct tta atg gca gct gat gtg ttt gaa aaa att cga   855
Asn Pro Lys Ile Ala Leu Met Ala Ala Asp Val Phe Glu Lys Ile Arg
    205                 210                 215

gtg aat cca gga aat tat gtt gat gga aga aaa aaa tgg ata gat aaa   903
Val Asn Pro Gly Asn Tyr Val Asp Gly Arg Lys Lys Trp Ile Asp Lys
220                 225                 230                 235

gtt tat aaa act aaa gaa gaa ttt gat gaa ggg aaa tta ttt ata aaa   951
Val Tyr Lys Thr Lys Glu Glu Phe Asp Glu Gly Lys Leu Phe Ile Lys
                240                 245                 250
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gaa aaa ttt gta cca tta att gaa aaa tgt aaa aga tta aat aga gca   999
Glu Lys Phe Val Pro Leu Il  Glu Lys Cys Lys Arg Leu Asn Arg Ala
            255                 260                 265

ata aga att gga aca aat cat gga tcc ctt tca tct cga gta tta tca  1047
Ile Arg Ile Gly Thr Asn His Gly Ser Leu Ser Ser Arg Val Leu Ser
        270                 275                 280

tat tat gga gat aca cca tta ggt atg gta gaa tcg gct ttt gag ttt  1095
Tyr Tyr Gly Asp Thr Pro Leu Gly Met Val Glu Ser Ala Phe Glu Phe
    285                 290                 295

tct gat tta tgt att gaa aac aat ttt tac aat ctt gtt ttt tct atg  1143
Ser Asp Leu Cys Ile Glu Asn Asn Phe Tyr Asn Leu Val Phe Ser Met
300                 305                 310                 315

aaa gct tct aat gct tat gtt atg ata caa tct tat aga tta tta gta  1191
Lys Ala Ser Asn Ala Tyr Val Met Ile Gln Ser Tyr Arg Leu Leu Val
                320                 325                 330

tct aaa caa tat gaa aga aat atg atg ttc cct ata cat tta gga gtt  1239
Ser Lys Gln Tyr Glu Arg Asn Met Met Phe Pro Ile His Leu Gly Val
            335                 340                 345

aca gaa gca gga ttt ggt gat aat gga aga ata aaa tct tat tta ggt  1287
Thr Glu Ala Gly Phe Gly Asp Asn Gly Arg Ile Lys Ser Tyr Leu Gly
        350                 355                 360

ata gga tct tta tta tat gat ggt ata gga gat acc att cgt ata tcc  1335
Ile Gly Ser Leu Leu Tyr Asp Gly Ile Gly Asp Thr Ile Arg Ile Ser
    365                 370                 375

tta aca gaa gat cct tgg gaa gag tta act cct tgt aaa aaa tta gtt  1383
Leu Thr Glu Asp Pro Trp Glu Glu Leu Thr Pro Cys Lys Lys Leu Val
380                 385                 390                 395

gaa aat tta aag aaa aga ata ttt tat aat gaa aat ttt aaa gaa gat  1431
Glu Asn Leu Lys Lys Arg Ile Phe Tyr Asn Glu Asn Phe Lys Glu Asp
                400                 405                 410

aat gaa tta aaa aat aat gaa atg gat acc aaa aat cta tta aat ttt  1479
Asn Glu Leu Lys Asn Asn Glu Met Asp Thr Lys Asn Leu Leu Asn Phe
            415                 420                 425

gaa gaa aat tat cga aat ttt aat aat ata aaa aaa aga aat gta gaa  1527
Glu Glu Asn Tyr Arg Asn Phe Asn Asn Ile Lys Lys Arg Asn Val Glu
        430                 435                 440

aaa aat aat aat gta tta cat gaa gag tgc act ata ggt aat gta gta  1575
Lys Asn Asn Asn Val Leu His Glu Glu Cys Thr Ile Gly Asn Val Val
    445                 450                 455

acc ata aaa gag tta gaa gat tct ctg caa att ttt aaa gat tta aat  1623
Thr Ile Lys Glu Leu Glu Asp Ser Leu Gln Ile Phe Lys Asp Leu Asn
460                 465                 470                 475
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tta gaa gta gat tca aat gga aat ttg aaa aag gga gcc aaa aca act   1671
Leu Glu Val Asp Ser Asn Gly Asn Leu Lys Lys Gly Ala Lys Thr Thr
                480                 485                 490

gat atg gtt att ata aat gat ttt cat aat ata aca aat tta gga aaa   1719
Asp Met Val Ile Ile Asn Asp Phe His Asn Ile Thr Asn Leu Gly Lys
            495                 500                 505

aaa act gtg gat aaa tta atg caa gtg gga att aat ata gta gtt caa   1767
Lys Thr Val Asp Lys Leu Met Gln Val Gly Ile Asn Ile Val Val Gln
        510                 515                 520

tat gaa cca cat aat ata gaa ttt ata gaa aaa atg gaa cca aat aat   1815
Tyr Glu Pro His Asn Ile Glu Phe Ile Glu Lys Met Glu Pro Asn Asn
    525                 530                 535

gat aat aat aat aat aat aat aat aat aat aat ata tta ttt tat gtg gat   1863
Asp Asn Asn Asn Asn Asn Asn Asn Asn Asn Ile Leu Phe Tyr Val Asp
540                 545                 550                 555

ata aaa aat att atg aac agt tca gaa aaa aat att aaa tta agt aat   1911
Ile Lys Asn Ile Met Asn Ser Ser Glu Lys Asn Ile Lys Leu Ser Asn
                560                 565                 570

tct aaa gga tat gga tta att tta aac gga aaa gaa gat ata caa acc   1959
Ser Lys Gly Tyr Gly Leu Ile Leu Asn Gly Lys Glu Asp Ile Gln Thr
            575                 580                 585

ata aaa aaa ata aaa gaa tta aat cgt cgt cct tta ttc att cta tta   2007
Ile Lys Lys Ile Lys Glu Leu Asn Arg Arg Pro Leu Phe Ile Leu Leu
        590                 595                 600

aaa tca gat aac ata tat gaa cat gta tta ata acc aga aga att aat   2055
Lys Ser Asp Asn Ile Tyr Glu His Val Leu Ile Thr Arg Arg Ile Asn
    605                 610                 615

gaa ctt tta caa tcc tta aat ata aat ata cct tat ata cat tat gtt   2103
Glu Leu Leu Gln Ser Leu Asn Ile Asn Ile Pro Tyr Ile His Tyr Val
620                 625                 630                 635

gat att aat tca aac aat tat gat gat ata tta gtt aat tca aca tta   2151
Asp Ile Asn Ser Asn Asn Tyr Asp Asp Ile Leu Val Asn Ser Thr Leu
                640                 645                 650

tat gca gga agt tgt ttg atg gat tta atg ggg gat ggt ctt att gtt   2199
Tyr Ala Gly Ser Cys Leu Met Asp Leu Met Gly Asp Gly Leu Ile Val
            655                 660                 665

aac gta act aat gat gtt ctt aca aat aaa aaa aag ata gaa aca aaa   2247
Asn Val Thr Asn Asp Val Leu Thr Asn Lys Lys Lys Ile Glu Thr Lys
        670                 675                 680

tat gat gaa aaa gaa gaa gta gag gaa gag gga aac aat aaa gat att   2295
Tyr Asp Glu Lys Glu Glu Val Glu Glu Glu Gly Asn Asn Lys Asp Ile
    685                 690                 695
```

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cat aga ctt ttg agc aga gtt gca tta aat tca ttt tta aca tta aat   2343
His Arg Leu Leu Ser Arg Val Ala L u Asn Ser Phe Leu Thr Leu Asn
700                 705                 710                 715

att tta caa gat aca aga ata cgt tta ttt aaa aca gat tat ata gcc   2391
Ile Leu Gln Asp Thr Arg Ile Arg Leu Phe Lys Thr Asp Tyr Ile Ala
                720                 725                 730

tgc cca tct tgt gga aga act tta ttt aat ata caa gaa act act aaa   2439
Cys Pro Ser Cys Gly Arg Thr Leu Phe Asn Ile Gln Glu Thr Thr Lys
            735                 740                 745

aaa att atg aaa tta aca ggg cac tta aaa ggc gtt aaa att gca gtc   2487
Lys Ile Met Lys Leu Thr Gly His Leu Lys Gly Val Lys Ile Ala Val
        750                 755                 760

atg gga tgt att gtt aat ggt ata gga gaa atg gca gat gca cat ttt   2535
Met Gly Cys Ile Val Asn Gly Ile Gly Glu Met Ala Asp Ala His Phe
    765                 770                 775

ggt tat gtt ggt agt gca cct aaa aaa att gat tta tat tat ggt aaa   2583
Gly Tyr Val Gly Ser Ala Pro Lys Lys Ile Asp Leu Tyr Tyr Gly Lys
780                 785                 790                 795

gag tta gta gaa aga aat ata cct gag gaa gaa gct tgt gat aaa ttg   2631
Glu Leu Val Glu Arg Asn Ile Pro Glu Glu Glu Ala Cys Asp Lys Leu
                800                 805                 810

ata gaa tta att aaa aaa cat aac aaa tgg aaa gat cca taaattgaat    2680
Ile Glu Leu Ile Lys Lys His Asn Lys Trp Lys Asp Pro
            815                 820

atggacaagt atttatttat ttatttatct tatatataat atattataaa tttttcgatg 2740

tatttttcct tttaaaattt tatttttttt ttatttttt ttttgaagta atatttataa 2800

tgcatacata atattaaaat gtgtattata taataatatc attttattgt tattttaaaa 2860

gactaatacc aagaacaatt ttttaataat cattcttata acttgttaaa tatatatata 2920

tatatatata tatttattta tttatattta tatttattta tttttggtat atgaaaagta 2980

aaaatataat aatttaaaag tatttacaaa ataaataata ttatatatct gtttttatat 3040

atatgttaat ggaaaaggag aaaataaata aataaaacaa acaaaataac atatatatat 3100

atatatatat actgaatgag aaagaaaaaa aaaagaaaag gatacga               3147
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  1               5                  10                  15
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```
His Val Lys Ile Lys Lys Leu Phe Ile Lys Ile Ser Asn Val Asn Ile
            20                  25                  30

Phe Phe Ala Glu Ala Lys Lys Asn Gly Lys Lys Glu Phe Phe Leu Phe
        35                  40                  45

Leu Leu Asn Ile Lys Lys Asn Ser Gln Gln Lys Lys Thr Tyr His Ile
    50                  55                  60

Thr Lys Arg Asn Thr Ile Asn Lys Ser Asp Phe Leu Tyr Ser Leu Leu
65                  70                  75                  80

Asn Glu Glu Gly Asn Ser Ser Lys Lys Glu Tyr Lys Asn Leu Lys Asp
                85                  90                  95

Glu Glu Lys Tyr Asn Ile Ile Gln Asn Ile Lys Lys Tyr Cys Glu Cys
            100                 105                 110

Thr Lys Lys Tyr Lys Arg Leu Pro Thr Arg Glu Val Val Ile Gly Asn
        115                 120                 125

Val Lys Ile Gly Gly Asn Asn Lys Ile Ala Ile Gln Thr Met Ala Ser
    130                 135                 140

Cys Asp Thr Arg Asn Val Glu Glu Cys Val Tyr Gln Ile Arg Lys Cys
145                 150                 155                 160

Lys Asp Leu Gly Ala Asp Ile Val Arg Leu Thr Val Gln Gly Val Gln
                165                 170                 175

Glu Ala Gln Ala Ser Tyr His Ile Lys Glu Lys Leu Leu Ser Glu Asn
            180                 185                 190

Val Asn Ile Pro Leu Val Ala Asp Ile His Phe Asn Pro Lys Ile Ala
        195                 200                 205

Leu Met Ala Ala Asp Val Phe Glu Lys Ile Arg Val Asn Pro Gly Asn
    210                 215                 220

Tyr Val Asp Gly Arg Lys Lys Trp Ile Asp Lys Val Tyr Lys Thr Lys
225                 230                 235                 240

Glu Glu Phe Asp Glu Gly Lys Leu Phe Ile Lys Glu Lys Phe Val Pro
                245                 250                 255

L u Ile Glu Lys Cys Lys Arg Leu Asn Arg Ala Ile Arg Ile Gly Thr
            260                 265                 270

Asn His Gly Ser Leu Ser Ser Arg Val Leu Ser Tyr Tyr Gly Asp Thr
        275                 280                 285

Pro Leu Gly Met Val Glu Ser Ala Phe Glu Phe Ser Asp Leu Cys Ile
    290                 295                 300

Glu Asn Asn Phe Tyr Asn Leu Val Phe Ser Met Lys Ala Ser Asn Ala
305                 310                 315                 320

Tyr Val Met Ile Gln Ser Tyr Arg Leu Leu Val Ser Lys Gln Tyr Glu
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325 330 335

Arg Asn Met Met Phe Pro Ile His Leu Gly Val Thr Glu Ala Gly Phe
340 345 350

Gly Asp Asn Gly Arg Ile Lys Ser Tyr Leu Gly Ile Gly Ser Leu Leu
355 360 365

Tyr Asp Gly Ile Gly Asp Thr Ile Arg Ile Ser Leu Thr Glu Asp Pro
370 375 380

Trp Glu Glu Leu Thr Pro Cys Lys Lys Leu Val Glu Asn Leu Lys Lys
385 390 395 400

Arg Ile Phe Tyr Asn Glu Asn Phe Lys Glu Asp Asn Glu Leu Lys Asn
405 410 415

Asn Glu Met Asp Thr Lys Asn Leu Leu Asn Phe Glu Glu Asn Tyr Arg
420 425 430

Asn Phe Asn Asn Ile Lys Lys Arg Asn Val Glu Lys Asn Asn Asn Val
435 440 445

Leu His Glu Glu Cys Thr Ile Gly Asn Val Val Thr Ile Lys Glu Leu
450 455 460

Glu Asp Ser Leu Gln Ile Phe Lys Asp Leu Asn Leu Glu Val Asp Ser
465 470 475 480

Asn Gly Asn Leu Lys Lys Gly Ala Lys Thr Thr Asp Met Val Ile Ile
485 490 495

Asn Asp Phe His Asn Ile Thr Asn Leu Gly Lys Lys Thr Val Asp Lys
500 505 510

Leu Met Gln Val Gly Ile Asn Ile Val Val Gln Tyr Glu Pro His Asn
515 520 525

Ile Glu Phe Ile Glu Lys Met Glu Pro Asn Asn Asp Asn Asn Asn Asn
530 535 540

Asn Asn Asn Asn Asn Ile Leu Phe Tyr Val Asp Ile Lys Asn Ile Met
545 550 555 560

Asn Ser Ser Glu Lys Asn Ile Lys Leu Ser Asn Ser Lys Gly Tyr Gly
565 570 575

Leu Ile Leu Asn Gly Lys Glu Asp Ile Gln Thr Ile Lys Lys Ile Lys
580 585 590

Glu Leu Asn Arg Arg Pro Leu Phe Ile Leu Leu Lys Ser Asp Asn Ile
595 600 605

Tyr Glu His Val Leu Ile Thr Arg Arg Ile Asn Glu Leu Leu Gln Ser
610 615 620

Leu Asn Ile Asn Ile Pro Tyr Ile His Tyr Val Asp Ile Asn Ser Asn
625 630 635 640

```
Asn Tyr Asp Asp Ile Leu Val Asn Ser Thr Leu Tyr Ala Gly Ser Cys
                645                 650                 655

Leu Met Asp Leu Met Gly Asp Gly Leu Ile Val Asn Val Thr Asn Asp
            660                 665                 670

Val Leu Thr Asn Lys Lys Lys Ile Glu Thr Lys Tyr Asp Glu Lys Glu
        675                 680                 685

Glu Val Glu Glu Glu Gly Asn Asn Lys Asp Ile His Arg Leu Leu Ser
    690                 695                 700

Arg Val Ala Leu Asn Ser Phe Leu Thr Leu Asn Ile Leu Gln Asp Thr
705                 710                 715                 720

Arg Ile Arg Leu Phe Lys Thr Asp Tyr Ile Ala Cys Pro Ser Cys Gly
                725                 730                 735

Arg Thr Leu Phe Asn Ile Gln Glu Thr Thr Lys Lys Ile Met Lys Leu
            740                 745                 750

Thr Gly His Leu Lys Gly Val Lys Ile Ala Val Met Gly Cys Ile Val
        755                 760                 765

Asn Gly Ile Gly Glu Met Ala Asp Ala His Phe Gly Tyr Val Gly Ser
    770                 775                 780

Ala Pro Lys Lys Ile Asp Leu Tyr Tyr Gly Lys Glu Leu Val Glu Arg
785                 790                 795                 800

Asn Ile Pro Glu Glu Glu Ala Cys Asp Lys Leu Ile Glu Leu Ile Lys
                805                 810                 815

Lys His Asn Lys Trp Lys Asp Pro
            820
```